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Antimicrobial Resistance to Agents Used for *Staphylococcus aureus* Decolonization: Is There a Reason for Concern?

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Abstract

Purpose of Review—Chlorhexidine gluconate (CHG) and mupirocin are increasingly used for *Staphylococcus aureus* decolonization to prevent healthcare-associated infections; however, increased use of these agents has led to concerns for growing resistance and reduced efficacy. In this review, we describe current understanding of reduced susceptibility to CHG and mupirocin in *S. aureus* and their potential clinical implications.

Recent Findings—While emergence of *S. aureus* tolerant or resistant to topical antimicrobial agents used for decolonization is well described, the clinical impact of reduced susceptibility is not clear. Important challenges are that standardized methods of resistance testing and interpretation are not established, and the risk for selection for co- or cross-resistance using universal, as opposed to targeted decolonization, is unclear.

Summary—Evidence continues to support *S. aureus* decolonization in certain patient groups, although further studies are needed to determine the long-term impact of CHG and mupirocin resistance on efficacy. Strategies to mitigate further development of reduced susceptibility and the consequences of selection pressures through universal decolonization on resistance will benefit from further investigation.

Keywords

Antimicrobial resistance; Antiseptic; Chlorhexidine; Mupirocin; Decolonization; *Staphylococcus aureus*

Introduction

Staphylococcus aureus colonization of the nares occurs in approximately 20–40% of patients [1–3] and imparts a three-to sixfold increased risk of healthcare-associated infection (HAI) due to *S. aureus* [2], leading to increased length of stay and cost compared to non-colonized

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patients [4]. Most HAIs caused by *S. aureus* are due to strains carried by patients before they developed infection [5]. Consequently, over the last several decades, clinicians have sought to reduce *S. aureus* HAIs by eliminating *S. aureus* carriage. Interest in decolonization grew further as the prevalence of methicillin-resistant *S. aureus* (MRSA) dramatically rose in hospitals and then communities around the world. Patients who carry MRSA are fourfold more likely to have MRSA infection (compared to patients colonized with methicillin-sensitive *S. aureus* (MSSA)) [6], suffer 30% higher 30-day mortality [7], and serve as a reservoir for transmission to other patients and the community.

Decolonization refers to the elimination of carriage or reduction of the microbial burden of one or more pathogens from the body through the use of biocidal agents [8]. Decolonization strategies may be targeted to colonized patients or given universally to all patients. Topical chlorhexidine gluconate (CHG) (given as a bath or using impregnated wipes) and/or topical mupirocin ointment (typically 2% concentration, administered intranasally two to three times daily for 5–7 days) for *S. aureus* decolonization have been shown to reduce HAIs and are widely utilized in multiple healthcare settings. CHG is used for additional healthcare applications including hand hygiene, periprocedural disinfection, and for the prevention of central line-associated bloodstream infections (CLABSI) infections through impregnated dressings.

Topical agents have many advantages over systemic agents. For example, they limit systemic exposure while achieving high concentrations at the site of bacteria. Furthermore, the biocidal activity of CHG persists long after application compared to other antiseptics [9]. However, with increased use, reduced bacterial susceptibility to these compounds has emerged. Whether this reduced susceptibility is clinically meaningful is not certain but may depend on the agent, the degree of nonsusceptibility, and the application.

In this review, we summarize the emergence of *S. aureus* resistance to CHG and mupirocin in the context of their use for decolonization. We then focus on potential implications and evidence for reduced efficacy, consider the potential clinical implications of universal decolonization strategies on resistance, and conclude by posing questions and research that may guide thoughtful use and potential alternatives to CHG and mupirocin for the prevention of *S. aureus*-related healthcare-associated infections in the future. CHG and mupirocin are studied and employed most extensively in the context of *S. aureus* decolonization; thus, the scope of this review will be *S. aureus* resistance with only a limited discussion of non-staphylococcal resistance.

The Importance of Mupirocin and Chlorhexidine Gluconate for Decolonization and Prevention of HAIs

An estimated 720,000 HAIs occur each year in US hospitals, for which *S. aureus* is the second leading causative pathogen (behind *Clostridium difficile*) and the most common identifiable cause of healthcare-associated surgical site infections [10]. HAIs due to MRSA are associated with two to three times the risk of 30-day mortality compared to patients without MRSA infection [7].

Level 1 evidence supports *S. aureus* decolonization in ICU patients to reduce MRSA colonization and bloodstream infections [11, 12•, 13, 14]. Evidence-based guidelines also recommend *S. aureus* decolonization of perioperative surgical patients for prevention of surgical site infections [15, 16], especially cardiothoracic and orthopedic surgeries [17]. The benefits of *S. aureus* decolonization in other non-ICU, non-surgical inpatient settings outside of certain high-risk patient populations (e.g., hemodialysis [18] or with central venous catheters[19]), remain to be determined [20].

Review of Chlorhexidine Gluconate Resistance and Influencing Factors

Developed in the 1950s, CHG is an antiseptic with broad biocidal activity including gram-positive and gram-negative bacteria, fungi, and enveloped viruses [21]. The bactericidal mechanism of CHG is thought to act through binding the cell wall, leading to osmotic disruption and cell death (Fig. 1) [22]. CHG is the water soluble form of a divalent cationic biguanide [23] and is generally regarded as safe and well tolerated when applied topically (typical concentrations ranging from 0.5 to 4%) [22], although rare allergic reactions have been reported [24]. With this strong safety and tolerability record, CHG is a mainstay antiseptic used in a wide range of healthcare products, including oral care rinses, hand hygiene rubs, soaps, CHG-impregnated catheter dressings, and CHG-impregnated catheters [25••, 26–28]. CHG-alcohol prepping solution is the preferred agent for skin antisepsis prior to central venous catheter placement or surgery [29].

S. aureus resistance to CHG is thought to occur primarily through efflux pumps [30•] encoded by quaternary ammonium compound (*qac*) genes, particularly *qacA* and *qacB* [31]; however, their exact role in CHG resistance is not well understood. Although the lack of a standard definition for CHG susceptibility prevents comparability of data in many cases, studies using internally valid methodologies suggest CHG resistance increases over time with widespread use [32, 33•]. A summary of the definitions, mechanisms, and prevalence of *S. aureus* CHG resistance is in Table 1.

Limitations to Defining CHG Resistance

Phenotypic CHG resistance is most commonly defined as a minimum inhibitory concentration (MIC) ≥ 4 μg/mL by broth dilution; however, this definition is not standardized and may not be clinically relevant [38]. The use of MIC to determine CHG resistance has been questioned for several reasons. First, the inhibitory effects are less important than the bactericidal effects of an antiseptic, such as CHG. Second, broth dilution does not take into account the significant residual biocidal activity of CHG over time [9]. Third, CHG concentrations attained topically are orders of magnitude higher than those considered to represent CHG resistance. For example, a 0.5% CHG aqueous solution equates to roughly 5,000 μg/mL [38]. It has been noted that the term “resistance” may be an inaccurate term for biocides like CHG [38]. While some microbes, like spores, are intrinsically non-susceptible to CHG [25••], others can survive at least lower concentrations of CHG (e.g., 4 μg/mL), due to persistence in the protective environment of a biofilm (“phenotypic tolerance”) [41] or through overexpression of efflux pumps (“chlorhexidine tolerance”) [42, 49]. Consequently, some prefer the term “reduced susceptibility” [38] or

"tolerance" [39] rather than resistance. For purposes of simplicity and consistency, we will refer to CHG resistance in this review.

The presence of *qacA/B* is often used as a marker or surrogate for phenotypic CHG resistance; however, the relationship between genotypic and phenotypic resistance is inconsistent. These discrepancies may be due to the inability of *qacB* (which is genetically difficult to distinguish from *qacA* without sequence analysis) to interact with CHG as a substrate or the presence of other multidrug efflux pumps active against CHG [34••].

Review of Mupirocin Resistance and Influencing Factors

Mupirocin, previously known as pseudomonic acid A, is a naturally occurring antibiotic produced by the soil bacterium *Pseudomonas fluorescens* that inhibits bacterial isoleucyl t-RNA synthetase (Fig. 1) [50]. The spectrum of clinically useful antibacterial activity of mupirocin includes broad gram-positive coverage, including methicillin-resistant *S. aureus* (MRSA). Mupirocin is rapidly metabolized and rendered in-active in the body, limiting its clinical use to topical applications, primarily nasal decolonization of *S. aureus* and impetigo.

Low levels of mupirocin in the environment are thought to generate a state of amino acid starvation, thereby increasing mutation rates and promoting acquisition of resistance that can spread either through clonal transmission or plasmid-mediated horizontal transfer from other bacteria, such as coagulase-negative staphylococci (CoNS).

The development of mupirocin resistance associated with widespread use of the antibiotic is well documented [51]. For example, one hospital observed the prevalence of mupirocin resistance among MRSA isolates rise from 2.7% at baseline to 65% 18 months after implementation of a universal mupirocin-based decolonization protocol [52]. Conversely, a Brazilian hospital saw the prevalence of high-level mupirocin resistance among MRSA clinical isolates fall from 44 to just 6% after instituting a policy restricting mupirocin use (from unrestricted use in all patients with MRSA colonization or infection plus treatment of skin infections to use only for targeted decolonization) [53]. The use of mupirocin to treat skin and soft tissue infections also promotes mupirocin resistance [54], and its role in treatment of impetigo has been questioned [55].

Similar to hospitals, communities with easy mupirocin access (e.g., over-the counter availability) have a high prevalence of mupirocin resistance [56]. At a Veterans Affairs Medical Center, the percentage of high-level mupirocin resistant MRSA isolates decreased from 31% during a period of unrestricted mupirocin use between 1990 and 1993 to 4% after strict "administrative control" of mupirocin prescriptions was implemented in 2000–2001 [57]. In New Zealand, unrestricted mupirocin use was associated with higher rates of resistance (28%) during a period of over-the-counter mupirocin availability from 1991 to 2000 [56] and resistance dropped significantly (to 11%) by 2013 following policy changes to restrict mupirocin use [58]. A summary of the definitions, mechanisms, and prevalence of *S. aureus* mupirocin resistance is in Table 2.

Clinical Implications of Reduced Susceptibility to *S. aureus* Decolonization Agents

While there is convincing evidence to suggest that decolonization strategies to control *S. aureus* using CHG and mupirocin promote resistance to these agents, the clinical implications of resistance in terms of decolonization failure, reduced efficacy to prevent HAIs, or development of co- or cross-resistance are unclear. For example, Suwantrarat and colleagues analyzed 150 CLABSI-related intensive care unit (ICU) clinical isolates and found 64% overall prevalence of CHG resistance in units without routine CHG bathing, compared to 86% among units with routine CHG bathing [33•]. Although the greatest reduction in CHG susceptibility associated with CHG bathing was seen among gram-positive bacteria, the overall number of CLABSI events declined and the proportion CLABSI due to *S. aureus* was lower in the units with CHG bathing (1 out of 16 gram-positive isolates (6.25%) in the CHG bathing group versus 19 *S. aureus* out of 65 gram-positive isolates (29%) in the non-CHG bathing group). Notably, enterococci were the most common isolate causing CLABSI in this study, 90% of which were CHG resistant; however, median CHG MICs were the same in both groups [33•].

Mupirocin resistance, particularly high-level resistance, is associated with decolonization failure [44, 69]. However, like CHG, the impact on efficacy in reducing HAIs is not clear in clinical studies. Furthermore, in vitro studies suggest the mupirocin resistance phenotype may come at a fitness cost in the absence of mupirocin [64].

While isolated CHG resistance is not directly associated with decolonization failure, the combination of *qacA/B* and low-level mupirocin resistance is shown to contribute to MRSA decolonization failure (defined as at least one positive weekly screening or clinical isolate within 1 year after decolonization) [70]. Although the impact of reduced decolonization failure on efficacy to prevent HAIs is unclear, the prevalence of *qacA/B* genes appear enriched among clinical isolates compared to isolates obtained for surveillance, suggesting a possible link to decolonization or disinfection failure, increased virulence, or antimicrobial co-resistance. For example, *qacA/B*-carrying *S. aureus* isolates are associated with invasive bloodstream infections [39] and Cho and colleagues found that ICU patients carrying *qacA/B*-positive MRSA were more likely have a clinical isolate (rather than just a surveillance MRSA isolate) and longer hospital stays compared to patients carrying *qacA/B*-negative MRSA [36]. In addition, non-*S. aureus* bacteria may develop resistance following exposure to CHG; for example, increased *Acinetobacter baumannii* and *Staphylococcus epidermidis* resistance to CHG were observed 1 year following institution of routine CHG bathing [71].

The development of co-resistance (horizontal transfer of resistance genes affecting susceptibility to other antimicrobials or antiseptics) between mupirocin, CHG, and/or other antimicrobials or antiseptics is a worrisome feature that may be potentiated through selection pressure by their widespread use. Plasmids carrying *qacA/B* genes have been identified in *S. epidermidis*, *Staphylococcus hominis*, *Listeria monocytogenes* [72], and carbapenem-resistant *Klebsiella pneumoniae* [73]. CHG and mupirocin co-resistance are known to occur via the pSK1 family of conjugative staphylococcal multidrug-resistance

plasmids [74], which may harbor resistance genes for other antibiotics such as β-lactams [75] and MRSA isolates are often less susceptible to CHG compared to methicillin-sensitive *S. aureus* (MSSA) [76]. Insertion sequences, particularly IS257, flanking the *mupA* gene may allow recombination to occur with chromosomal DNA [77].

Similarly troubling are several studies indicating that CHG resistance may promote antibiotic cross-resistance [38] defined as a resistance mechanism leading to resistance to more than one agent. In one in vitro evolution study, repeated exposures of CHG led to reduced susceptibility of vancomycin-resistant *Enterococcus faecium* isolates to daptomycin [78]. While CHG cross-resistance in *S. aureus* is controversial [30•, 79], MRSA strains have been associated with CHG [80] and mupirocin [81] resistance. Whether selection for methicillin resistance is caused by or simply associated with resistance these agents is not clear. Aside from antibiotics, efflux-mediated cross-resistance to other antiseptics used for hospital cleaning could theoretically occur; however, to our knowledge, inadequate environmental disinfection has not been associated with CHG resistance for bacteria not already known to be CHG tolerant (e.g., *Pseudomonas* and *Klebsiella* spp.) [82]. Given its unique mechanism of action, mupirocin cross-resistance to other clinically used antibiotics is not known to occur [83].

Universal Versus Targeted Decolonization Strategies

Debate exists whether decolonization strategies should best be implemented universally for all patients, regardless of their colonization status, or targeted to patients with identified *S. aureus* colonization. Universal decolonization may be less time intensive (without the necessity for screening nasal culture or PCR) and more efficacious but increased CHG and mupirocin exposure risks potentially worsening resistance. The REDUCE-MRSA three-arm, cluster-randomized trial of ICU patients at 43 hospitals compared screening plus isolation without decolonization, targeted decolonization of MRSA-colonized patients with CHG and mupirocin, or universal decolonization with CHG and mupirocin. Studying over 122,000 patients over 30 months, the study showed that universal decolonization was superior to targeted decolonization and screening plus isolation without decolonization in reducing MRSA infections (hazard ratios 0.92, 0.75, and 0.63, respectively) and all-cause bloodstream infections (hazard ratios 0.99, 0.78, and 0.56, respectively) [12•]. A universal decolonization strategy is proposed for prevention of surgical site infections as well [84•].

While the authors of the REDUCE-MRSA trial argue that universal decolonization may be more cost-effective, a meta-analysis published in 2009 found mupirocin to be cost effective only when a targeted decolonization approach was used [85]. In addition, universal decolonization may theoretically predispose towards the development of *S. aureus* antimicrobial resistance not only by selection of tolerant *S. aureus* clones but also through increased horizontal gene transfer from CoNS. In a separate study, in vivo transfer of plasmid-borne *mupA* between CoNS and MRSA was observed in a patient who developed high-level mupirocin-resistant MRSA during mupirocin treatment, suggesting that CoNS commensals may serve as an environmental reservoir for mupirocin resistance [86]. Consequently, some have advocated to limit mupirocin exposure to *S. aureus*-colonized patients in order to reduce the risk of emerging resistance [53]. However, a follow-up study

of 3,3173 MRSA isolates from the REDUCE-MRSA trial was performed to assess CHG and mupirocin resistance and found only 2 CHG-resistant isolates by broth dilution (defined as MIC ≥ 8 μg/mL), both occurring during periods without CHG/mupirocin decolonization [34••]. High-level mupirocin resistance was more common in the universal decolonization arm compared to the arms without decolonization or targeted decolonization; however, the difference was not statistically significant and the intervention period was short (18 months).

Mathematical models to evaluate the risk of resistance associated with universal decolonization show mixed findings. A model published by Hetem and colleagues (that accounted for ecological factors such as horizontal gene transmission from CoNS to *S. aureus*) concluded that the likelihood of worsening *S. aureus* mupirocin resistance through universal decolonization is negligible compared to a targeted decolonization strategy or no decolonization [84•]. However, a different model by Deeny and colleagues suggested that a universal decolonization could lead to a significantly higher prevalence of mupirocin resistance among MRSA strains compared to targeted decolonization after 5 years (21 versus 9% estimated prevalence of mupirocin resistance, respectively) [87•].

Alternative Decolonization Agents

With increasing resistance, alternative agents for decolonization may need to be considered. Investigational antibiotic or antiseptic alternatives for mupirocin-based *S. aureus* decolonization include neomycin, povidone-iodine, fusidic acid, triclosan, intranasal CHG, lysostaphin, ethanol, and omiganan pentahydrochloride; however, the clinical efficacy of these agents is largely unknown [25••, 61, 88•, 89, 90]. Among these agents, only intranasal povidone-iodine has been directly compared to mupirocin in arthroplasty and spine fusion patients and was equivalent for the prevention of SSIs when either intervention was combined with CHG skin wipes [91]. Relative efficacy of other agents will require head-to-head trials with mupirocin. Non-antibiotic/non-antiseptic alternatives that have been proposed include bacteriophage therapy [92], probiotics [93], medical-grade honey [61•, 94], and tea tree oil [61•]. If efficacious, these products would theoretically have an advantage of achieving decolonization without selecting for antimicrobial resistance.

As an alternative antiseptic to CHG, dilute sodium hypochlorite (bleach) bathing was shown to be superior to CHG (both combined with intranasal mupirocin) for *S. aureus* eradication in a randomized controlled trial [95]. Octenidine dihydrochloride (combined with mupirocin) has also been investigated as another potential CHG substitute [96], but a recent prospective crossover trial failed to demonstrate a benefit to octenidine dihydrochloride body washing to prevent MRSA acquisition or MRSA infection [97].

Systemic antibiotics have been used to enhance topical decolonization and could play a future role in the management of increasing resistance to decolonization agents. Parras and colleagues studied mupirocin versus intranasal fusidic acid plus oral trimethoprim/sulfamethoxazole (both in combination with CHG bathing) and found that they were equally effective for nasal MRSA decolonization [98]. Another study by Simor and colleagues demonstrated that oral antibiotics (rifampin and doxycycline for 7 days), in combination with CHG and mupirocin, successfully decolonized hospitalized MRSA-colonized patients

[69]. While the systemic antibiotic approach was not originally intended to combat CHG or mupirocin resistance but rather to address multisite, extranasal MRSA carriage such as gastrointestinal, perineum, or skin [61•], oral antibiotics may conceivably be used in certain high-risk populations identified as having CHG and/or mupirocin resistant strains in whom the benefits of effective decolonization may outweigh the risks of systemic antibiotic exposure or in whom decolonization protocols using mupirocin and CHG or dilute bleach have failed. However, the routine use of oral antibiotics for *S. aureus* eradication is not recommended by current IDSA Clinical Practice Guidelines [99].

Discussion

CHG and mupirocin remain cornerstones for *S. aureus* decolonization for the prevention of HAIs; however, the emergence of resistance with widespread use raises questions about continued efficacy and implications for infection control. The development of CHG and mupirocin resistance associated with decolonization is poorly characterized and may be underappreciated. However, despite the association between resistance and increased decolonization failure, HAIs due to MRSA have in fact decreased by over 50% between 2005 and 2011 [100], despite increasing mupirocin and CHG resistance during this time [48, 51, 61•]. Reasons for retained decolonization efficacy may be because in vitro measures of resistance are clinically irrelevant or that trials are inadequately designed to account for the development of resistance over time.

Many studies demonstrating efficacy of decolonization to reduce infections failed to measure mupirocin or CHG susceptibility were performed in a background of low *S. aureus* resistance, or had a short follow-up period. For example, one of the largest multicenter randomized trials demonstrating the efficacy of perioperative nasal mupirocin/CHG decolonization involving 918 perioperative *S. aureus* colonized patients (showing a 56% reduced rate of *S. aureus* infection with decolonization compared to placebo) was performed in a population with a low background rate of *S. aureus* resistance; all 1,270 *S. aureus* nasal isolates collected in the study were methicillin and mupirocin susceptible [2]. Mupirocin resistance, which is expected to take several years to develop [87•], may not have had sufficient time to develop during the two year study [2]. Furthermore, CHG resistance was not measured.

Defining resistance is a challenge with no clear consensus definition for CHG or mupirocin resistance. In addition, MIC is an imperfect measure of phenotypic CHG resistance. Alternative CHG susceptibility methods have been proposed and deserve further scrutiny, including surface disinfection and residue testing [79], time-kill curve [101], epidemiologic cutoff values [30•, 102], and mean bactericidal concentration (MBC) [38]. On a molecular level, while the presence of *mupA* predicts mupirocin phenotypic resistance, the detection of efflux pump genes such as *qacA/B* likely provides an incomplete picture of CHG resistance. In addition to the difficulty of defining, detecting, and performing surveillance for mupirocin and CHG resistance, it is also unclear how resistance to these agents should influence clinical practice and what role, if any, there is for alternative options for decolonization.

Conclusion

S. aureus colonization is a well-recognized and modifiable risk factor for infections due to *S. aureus*. Evidence continues to support the use of CHG and mupirocin-based decolonization strategies to prevent HAIs, which are responsible for considerable morbidity and mortality among hospitalized patients. Despite the association between resistance and increased decolonization failure, HAIs due to MRSA have dropped over the last decade despite increased mupirocin and CHG use.

Although the clinical implications of *S. aureus* resistance to CHG and mupirocin are unclear, the potential epidemiologic risks including CHG co- or cross-resistance to other agents and horizontal transfer of resistance genes are considerable and warrant further study. Future studies examining the efficacy of CHG and mupirocin-based decolonization must be done with longer or delayed periods of follow-up in order to determine decolonization efficacy in settings with resistance.

In order to minimize selection pressure for the development and spread of resistance to CHG and mupirocin, it is reasonable to limit the use of these valuable agents for indications without established benefit, such as mupirocin for skin infections or over-the-counter use [2]. Similarly, some have called for “antiseptic stewardship” measures restricting non-evidence based CHG applications, such as eliminating CHG from alcohol-based rubs or soaps for routine hand hygiene [30•], which may help to control CHG resistance in the healthcare environment. Uncertainty remains whether the risks of increased resistance to these agents associated with universal decolonization (versus targeted decolonization) outweigh the possible benefits of feasibility, efficacy, and cost.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Wertheim HFL, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, et al. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5: 751–62. 10.1016/S1473-3099(05)70295-4. [PubMed: 16310147]
2. Bode LGM, Kluytmans JAJW, Wertheim HFL, Bogaers D, Vandenbroucke-Grauls CMJE, Roosendaal R, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med. 2010;362:9–17. 10.1056/NEJMoa0808939. [PubMed: 20054045]
3. Gorwitz RJ, Kruszon-Moran D, McAllister SK, McQuillan G, McDougal LK, Fosheim GE, et al. Changes in the prevalence of nasal colonization with Staphylococcus aureus in the United States, 2001–2004. J Infect Dis. 2008;197:1226–34. 10.1086/533494. [PubMed: 18422434]
4. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol. 2005;26:166–74. 10.1086/502522. [PubMed: 15756888]
5. Eiff v C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. N Engl J Med. 2001;344:11–6. 10.1056/NEJM200101043440102. [PubMed: 11136954]

6. Safdar N, Bradley EA. The risk of infection after nasal colonization with Staphylococcus aureus. Am J Med. 2008;121:310–5. 10.1016/j.amjmed.2007.07.034. [PubMed: 18374690]
7. Nelson RE, Slayton RB, Stevens VW, Jones MM, Khader K, Rubin MA, et al. Attributable mortality of healthcare-associated infections due to multidrug-resistant gram-negative bacteria and methicillin-resistant Staphylococcus aureus. Infect Control Hosp Epidemiol. 2017;38:848–56. 10.1017/ice.2017.83. [PubMed: 28566096]
8. Calfee DP. Prevention and control of health care-associated infections. Twenty-Fifth Edition Elsevier Inc. 2016 pp. 1861–1863. doi:10.1016/B978-1-4557-5017-7.00282-8.
9. Lowbury EJ, Lilly HA. Use of 4 percent chlorhexidine detergent solution (Hibiscrub) and other methods of skin disinfection. Br Med J. 1973;1:510–5. [PubMed: 4692674]
10. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370:1198–208. 10.1056/NEJMoa1306801. [PubMed: 24670166]
11. Ridenour G, Lampen R, Federspiel J, Kritchevsky S, Wong E, Climo M. Selective use of intranasal mupirocin and chlorhexidine bathing and the incidence of methicillin-resistant Staphylococcus aureus colonization and infection among intensive care unit patients. Infect Control Hosp Epidemiol. 2007;28:1155–61. 10.1086/520102. [PubMed: 17828692]
12•. Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013;368:2255–65. 10.1056/NEJMoa1207290. [PubMed: 23718152] The largest randomized trial to date examining universal versus targeted S. aureus decolonization of ICU patients.
13. Yokoe DS, Anderson DJ, Berenholtz SM, Calfee DP, Dubberke ER, Ellingson KD, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Infect Control Hosp Epidemiol. 2014;35(Suppl 2):S21–31. 10.1086/677216. [PubMed: 25376067]
14. Milstone AM, Elward A, Song X, Zerr DM, Orscheln R, Speck K, et al. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial. Lancet. 2013;381:1099–106. 10.1016/S0140-6736(12)61687-0. [PubMed: 23363666]
15. Anderson DJ, Podgorny K, Berríos-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2016;35:S66–88. 10.1017/S0899823X00193869.
16. Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt). 2013;14:73–156. 10.1089/sur.2013.9999. [PubMed: 23461695]
17. Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis Elsevier. 2016;16:e276–87. 10.1016/S1473-3099(16)30398-X.
18. Kluytmans J, Manders MJ. Elimination of nasal carriage of Staphylococcus aureus in hemodialysis patients. Infect Control Hosp Epidemiol. 1996;17:793–7. 10.1017/S0195941700003507. [PubMed: 8985765]
19. Mimoz O, Lucet J-C, Kerforne T, Pascal J, Souweine B, Goudet V, et al. Skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. Lancet. 2015;386:2069–77. 10.1016/S0140-6736(15)00244-5. [PubMed: 26388532]
20. Huang SS, Septimus E, Kleinman K. Daily chlorhexidine bathing in general hospital units—results of the ABATE Infection Trial (Active BAThing to Eliminate Infection). Open Forum Infect Dis. 2017;(Suppl 1):S35–7. 10.4103/0976-237X.188554.
21. Gantait S, Bhattacharyya J, Das S, Biswas S, Ghati A, Ghosh S, et al. Comparative assessment of the effectiveness of different cleaning methods on the growth of Candida albicans over acrylic surface. Contemp Clin Dent Medknow Publications. 2016;7:336–42. 10.4103/0976-237X.188554.

22. Milstone AM, Passaretti CL, Perl TM. Chlorhexidine: expanding the armamentarium for infection control and prevention. Clin Infect Dis. 2008;46:274–81. 10.1086/524736. [PubMed: 18171263]

23. Davies GE, Francis J, Martin AR, Rose FL, Swain G. 1: 6-DI-4′-Chlorhophenyldiguanidohexane ("Hibitane"). Laboratory investigation of a new antibacterial agent of high potency. Br J Pharmacol Chemother. 1954;9:192–6. 10.1111/j.1476-5381.1954.tb00840.x. [PubMed: 13172429]

24. Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. ANZ J Surg. 2016;86: 237–43. 10.1111/ans.13269. [PubMed: 26361890]

25••. Williamson DA, Carter GP, Howden BP. Current and Emerging topical antibacterials and antiseptics: agents, action, and resistance patterns. Clin Microbiol Rev. 2017;30:827–60. 10.1128/CMR.00112-16. [PubMed: 28592405] A comprehensive review of patterns and mechanisms of resistance to topical biocides.

26. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control. 2011;39(4Suppl 1):S1–S34. 10.1016/j.ajic.2011.01.003. [PubMed: 21511081]

27. Safdar N, O'Horo JC, Ghufran A, Bearden A, Didier ME, Chateau D, et al. Chlorhexidine-impregnated dressing for prevention of catheter-related bloodstream infection. Crit Care Med. 2014;42: 1703–13. 10.1097/CCM.0000000000000319. [PubMed: 24674924]

28. Rupp ME. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections. Ann Intensive Care. 2005;143:570 10.7326/0003-4819-143-8-200510180-00007.

29. Darouiche RO, Wall MJ, Itani KMF, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med. 2010;362:18–26. 10.1056/NEJMoa0810988. [PubMed: 20054046]

30•. Kampf G Acquired resistance to chlorhexidine—is it time to establish an "antiseptic stewardship" initiative? J Hosp Infect. 2016;94:213–27. 10.1016/j.jhin.2016.08.018. [PubMed: 27671220] Proposal for an "antiseptic stewardship" initiative to limit CHG use.

31. Smith K, Gemmell CG, Hunter IS. The association between biocide tolerance and the presence or absence of qac genes among hospital-acquired and community-acquired MRSA isolates. J Antimicrob Chemother. 2008;61:78–84. 10.1093/jac/dkm395. [PubMed: 17981834]

32. Wang JT, Sheng WH, Wang JL, Chen D, Chen ML, Chen YC, et al. Longitudinal analysis of chlorhexidine susceptibilities of nosocomial methicillin-resistant Staphylococcus aureus isolates at a teaching hospital in Taiwan. J Antimicrob Chemother. 2008;62: 514–7. 10.1093/jac/dkn208. [PubMed: 18477706]

33•. Suwantarat N, Carroll KC, Tekle T, Ross T, Maragakis LL, Cosgrove SE, et al. High prevalence of reduced chlorhexidine susceptibility in organisms causing central line-associated bloodstream infections. Infect Control Hosp Epidemiol. 2014;35:1183–6. [PubMed: 25111928] Study comparing prevalences of CHG resistance among CLABSI isolates in units with and without CHG bathing.

34••. Hayden MK, Lolans K, Haffenreffer K, Avery TR, Kleinman K, Li H, et al. Chlorhexidine and mupirocin susceptibility of methicillin-resistant Staphylococcus aureus isolates in the REDUCE-MRSA trial. J Clin Microbiol. 2016;54:2735–42. 10.1128/JCM.01444-16. [PubMed: 27558180] Largest published study to date assessing CHG and mupirocin resistance associated with implementation of universal versus targeted colonization.

35. Suller MTE, Russell AD. Antibiotic and biocide resistance in methicillin-resistant staphylococcus aureus and vancomycin-resistant Enterococcus. J Hosp Infect. 1999;43:281–91. 10.1016/S0195-6701(99)90424-3. [PubMed: 10658804]

36. Cho O-H, Park K-H, Song JY, Hong JM, Kim T, Hong SI, et al. Prevalence and microbiological characteristics of qacA/B-positive methicillin-resistant Staphylococcus aureus isolates in a surgical intensive care unit. Microb. Drug Resist 2017;00:1–7. 10.1089/mdr.2017.0072.

37. Warren DK, Prager M, Munigala S, Wallace MA, Kennedy CR, Bommarito KM, et al. Prevalence of qacA/B genes and mupirocin resistance among methicillin-resistant Staphylococcus aureus (MRSA) isolates in the setting of chlorhexidine bathing without mupirocin. Infect Control Hosp Epidemiol. 2016;37:590–7. 10.1017/ice.2016.1. [PubMed: 26828094]

38. Horner C, Mawer D, Wilcox M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? J Antimicrob Chemother. 2012;67:2547–59. 10.1086/677628. [PubMed: 22833635]
39. McNeil JC, Kok EY, Vallejo JG, Campbell JR, Hulten KG, Mason EO, et al. Clinical and molecular features of decreased chlorhexidine susceptibility among nosocomial Staphylococcus aureus isolates at Texas Children's Hospital. Antimicrob Agents Chemother. 2016;60:1121–8. 10.1128/AAC.02011-15. [PubMed: 26666947]
40. Best M, Sattar SA, Springthorpe VS, Kennedy ME. Efficacies of selected disinfectants against Mycobacterium tuberculosis. J Clin Microbiol. 1990;28:2234–9. [PubMed: 2121783]
41. Bonez PC, Santos Alves dos CF, Dalmolin TV, Agertt VA, Mizdal CR, Flores VDC, et al. Chlorhexidine activity against bacterial biofilms. Am J Infect Control. 2013;41:E119–22. 10.1016/j.ajic.2013.05.002. [PubMed: 23910527]
42. Skovgaard S, Larsen MH, Nielsen LN, Skov RL, Wong C, Westh H, et al. Recently introduced qacA/B genes in Staphylococcus epidermidis do not increase chlorhexidine MIC/MBC. J Antimicrob Chemother. 2013;68:2226–33. 10.1093/jac/dkt182. [PubMed: 23739538]
43. Choudhury MA, Sidjabat HE, Rathnayake IU, Gavin N, Chan RJ, Marsh N, et al. Culture-independent detection of chlorhexidine resistance genes qacA/B and smr in bacterial DNA recovered from body sites treated with chlorhexidine-containing dressings. J MedMicrobiol. 2017;66:447–53. 10.1099/jmm.0.000463.
44. Fritz SA, Hogan PG, Camins BC, Ainsworth AJ, Patrick C, Martin MS, et al. Mupirocin and chlorhexidine resistance in Staphylococcus aureus in patients with community-onset skin and soft tissue infections. Antimicrob Agents Chemother. 2013;57:559–68. 10.1128/AAC.01633-12. [PubMed: 23147738]
45. Schlett CD, Millar EV, Crawford KB, Cui T, Lanier JB, Tribble DR, et al. Prevalence of chlorhexidine-resistant methicillin-resistant Staphylococcus aureus following prolonged exposure. Antimicrob Agents Chemother. 2014;58:4404–10. 10.1128/AAC.02419-14. [PubMed: 24841265]
46. Lu Z, Chen Y, Chen W, Liu H, Song Q, Hu X, et al. Characteristics of qacA/B-positive Staphylococcus aureus isolated from patients and a hospital environment in China. J Antimicrob Chemother. 2014;70:653–7. 10.1093/jac/dku456. [PubMed: 25429780]
47. Hasanvand A, Ghafourian S, Taherikalani M, Jalilian FA, Sadeghifard N, Pakzad I. Antiseptic resistance in methicillin sensitive and methicillin resistant Staphylococcus aureus isolates from some major hospitals, Iran. Recent Pat Antiinfect Drug Discov. 2015;10:105–12. [PubMed: 26100979]
48. Jennings MC, Minbiole KPC, Wuest WM. Quaternary ammonium compounds: an antimicrobial mainstay and platform for innovation to address bacterial resistance. ACS Infect Dis. 2015;1: 288–303. 10.1021/acsinfecdis.5b00047. [PubMed: 27622819]
49. Wayne PA.Methods for determining bactericidal activity of antimicrobial agents: approved guideline. CLSI document M26-A. Clinical and Laboratory Standards Institute 1999.
50. Wuite J, Davies BI, Go M, Lambers J, Jackson D, Mellows G. Pseudomonic acid: a new topical antimicrobial agent. Lancet. 1983;2:394 10.1016/S0140-6736(83)90358-6. [PubMed: 6135884]
51. Simor AE, Stuart TL, Louie L, Watt C, Ofner-Agostini M, Gravel D, et al. Mupirocin-resistant, methicillin-resistant Staphylococcus aureus strains in Canadian hospitals. Antimicrob Agents Chemother. 2007;51:3880–6. 10.1128/AAC.00846-07. [PubMed: 17724154]
52. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant Staphylococcus aureus after widespread use of nasal mupirocin ointment. Infect Control Hosp Epidemiol. 1996;17:811–3. 10.1017/S019594170000357X. [PubMed: 8985769]
53. Vivoni AM, Santos K, de-Oliveira MP. Mupirocin for controlling methicillin-resistant Staphylococcus aureus: lessons from a decade of use at a university hospital. Infect Control Hosp Epidemiol. 2005;26:662–7. 10.1086/502599. [PubMed: 16092750]
54. Hetem DJ, Bonten MJM. Clinical relevance of mupirocin resistance in Staphylococcus aureus. J Hosp Infect. 2013;85:249–56. 10.1016/j.jhin.2013.09.006. [PubMed: 24144552]

55. Chaturvedi P, Singh AK, Shukla S, Agarwal L. Prevalence of mupirocin resistant Staphylococcus aureus isolates among patients admitted to a tertiary care hospital. N Am J Med Sci. 2014;6:403–7. 10.4103/1947-2714.139293. [PubMed: 25210674]

56. Mupirocin Upton A. and Staphylococcus aureus: a recent paradigm of emerging antibiotic resistance. J Antimicrob Chemother. 2003;51:613–7. 10.1093/jac/dkg127. [PubMed: 12615862]

57. Walker ES, Levy F, Shorman M, David G, Abdalla J, Sarubbi FA. A decline in mupirocin resistance in methicillin-resistant Staphylococcus aureus accompanied administrative control of prescriptions. J Clin Microbiol. 2004;42:2792–5. 10.1128/JCM.42.6.2792-2795.2004. [PubMed: 15184473]

58. Williamson DA, Monecke S. High usage of topical fusidic acid and rapid clonal expansion of fusidic acid-resistant Staphylococcus aureus: a cautionary tale. Clin Infect Dis. 2014;59:1451–4. 10.1093/cid/ciu658. [PubMed: 25139961]

59. Finlay JE, Miller LA, Poupard JA. Interpretive criteria for testing susceptibility of staphylococci to mupirocin. Antimicrob Agents Chemother. 1997;41:1137–9. [PubMed: 9145883]

60. European Committee On Antimicrobial Susceptibility Testing Website: Clinical Breakpoints [Internet]. eucast.org. [cited2017Nov 21]. Available from: http://www.eucast.org/clinical_breakpoints/

61•. Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. J Antimicrob Chemother. 2015;70:2681–92. 10.1093/jac/dkv169. [PubMed: 26142407] A review of potential alternative agents for mupirocin-based decolonization.

62•. Patel JB, Gorwitz RJ, Jernigan JA. Mupirocin resistance. Clin Infect Dis. 2009;49:935–41. 10.1086/605495. [PubMed: 19673644] Guidelines defining high versus low-level mupirocin resistance.

63••. Wayne PA. Performance standards for antimicrobial susceptibility testing, 26th edition. CLSI Supplement M100S. Clinical and Laboratory Standards Institute 2016.CLSI definitions for antimicrobial resistance, including mupirocin.

64. Lee AS, Gizard Y, Empel J, Bonetti E-J, Harbarth S, François P. Mupirocin-induced mutations in ileS in various genetic backgrounds of methicillin-resistant Staphylococcus aureus. J Clin Microbiol. 2014;52:3749–54. 10.1128/JCM.01010-14. [PubMed: 25122856]

65. Suwantarat N, Carroll KC, Tekle T, Ross T, Popoola VO, Milstone AM. Low prevalence of mupirocin resistance among hospital-acquired methicillin-resistant Staphylococcus aureus isolates in a neonatal intensive care unit with an active surveillance cultures and decolonization program. Infect Control Hosp Epidemiol. 2015;36:232–4. 10.1017/ice.2014.17. [PubMed: 25633010]

66. McDanel JS, Murphy CR, Diekema DJ, Quan V, Kim DS, Peterson EM, et al. Chlorhexidine and mupirocin susceptibilities of methicillin-resistant staphylococcus aureus from colonized nursing home residents. Antimicrob Agents Chemother. 2013;57:552–8. 10.1128/AAC.01623-12. [PubMed: 23147721]

67. Kresken M, Hafner D, Schmitz F-J, Wichelhaus TA. Prevalence of mupirocin resistance in clinical isolates of Staphylococcus aureus and Staphylococcus epidermidis: results of the Antimicrobial Resistance Surveillance Study of the Paul-Ehrlich-Society for Chemotherapy, 2001. Int J Antimicrob Agent. 2004;23:577–81. 10.1016/j.ijantimicag.2003.11.007.

68. Hamed G-M, van Belkum A, Awang H, van Wamel W, Vasanthakumari N. Methicillin-susceptible and -resistant Staphylococcus aureus with high-level antiseptic and low-level mupirocin resistance in Malaysia. Microb Drug Resist. 2014;20: 472–7. 10.1089/mdr.2013.0222. [PubMed: 24841796]

69. Simor AE, Phillips E, McGeer A, Konvalinka A, Loeb M, Devlin HR, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant Staphylococcus aureus colonization. Clin Infect Dis. 2007;44: 178–85. 10.1086/510392. [PubMed: 17173213]

70. Lee AS, Macedo-Vinas M, François P, Renzi G, Schrenzel J, Vernaz N, et al. Impact of combined low-level mupirocin and genotypic chlorhexidine resistance on persistent methicillin-resistant Staphylococcus aureus carriage after decolonization therapy: a case-control study. Clin Infect Dis. 2011;52:1422–30. 10.1093/cid/cir233. [PubMed: 21628482]

71. Apisarnthanarak A, Yang Hsu L, Lim T-P, Mundy LM. Increase in chlorhexidine minimal inhibitory concentration of Acinetobacter baumannii clinical isolates after implementation of advanced source control. Infect Control Hosp Epidemiol. 2014;35:98–9. 10.1086/674404. [PubMed: 24334810]

72. Wassenaar TM, Ussery D, Nielsen LN, Ingmer H. Review and phylogenetic analysis of qac genes that reduce susceptibility to quaternary ammonium compounds in Staphylococcus species. Eur J Microbiol Immunol. 2015;5:44–61. 10.1556/EUJMI-D-14-00038.

73. Azadpour M, Nowroozi J, Goudarzi GR, Mahmoudvand H. Presence of qacEΔ1 and cepA genes and susceptibility to a hospital biocide in clinical isolates of Klebsiella pneumoniae in Iran. Trop Biomed. 2015;32:109–15. [PubMed: 25801259]

74. Pérez-Roth E, López-Aguilar C, Alcoba-Flórez J, Méndez-Álvarez S. High-level mupirocin resistance within methicillin-resistant Staphylococcus aureus pandemic lineages. Antimicrob Agents Chemother. 2006;50:3207–11. 10.1128/AAC.00059-06. [PubMed: 16940133]

75. Jensen SO, Apisiridej S, Kwong SM, Yang YH, Skurray RA, Firth N. Analysis of the prototypical Staphylococcus aureus multiresistance plasmid pSK1. Plasmid. 2010;64:135–42. 10.1016/j.plasmid.2010.06.001. [PubMed: 20547176]

76. Kampf G, Jarosch R. Limited effectiveness of chlorhexidine based hand disinfectants against methicillin-resistant Staphylococcus aureus (MRSA). J Hosp Infect. 1998;38:297–303. 10.1016/S0195-6701(98)90078-0. [PubMed: 9602978]

77. Udo EE. A chromosomal location of the mupA gene in Staphylococcus aureus expressing high-level mupirocin resistance. J Antimicrob Chemother. 2003;51:1283–6. 10.1093/jac/dkg188. [PubMed: 12668579]

78. Bhardwaj P, Hans A, Ruikar K, Guan Z, Palmer KL. Reduced chlorhexidine and daptomycin susceptibility in vancomycin-resistant Enterococcus faecium after serial chlorhexidine exposure. Antimicrob Agents Chemother. 2018;62:e01235–17. 10.1128/AAC.01235-17. [PubMed: 29038276]

79. Vali L, Davies SE, Lai LLG, Dave J, Amyes SGB. Frequency of biocide resistance genes, antibiotic resistance and the effect of chlorhexidine exposure on clinical methicillin-resistant Staphylococcus aureus isolates. J Antimicrob Chemother. 2008;61:524–32. 10.1093/jac/dkm520. [PubMed: 18227090]

80. Otter JA, Patel A, Cliff PR, Halligan EP, Tosas O, Edgeworth JD. Selection for qacA carriage in CC22, but not CC30, methicillin-resistant Staphylococcus aureus bloodstream infection isolates during a successful institutional infection control programme. J Antimicrob Chemother. 2013;68:992–9. 10.1093/jac/dks500. [PubMed: 23288405]

81. Cadilla A, David MZ, Daum RS, Boyle-Vavra S. Association of high-level mupirocin resistance and multidrug-resistant methicillin-resistant Staphylococcus aureus at an academic center in the midwestern United States. J Clin Microbiol. 2011;49:95–100. 10.1128/JCM.00759-10. [PubMed: 21084520]

82. Farrand RJ, Williams A. Evaluation of single-use packs of hospital disinfectants. Lancet. 1973;1:591–3. 10.1016/S0140-6736(73)90730-7. [PubMed: 4120653]

83. Sutherland R, Boon RJ, Griffin KE, Masters PJ, Slocombe B, White AR. Antibacterial activity of mupirocin (pseudomonic acid), a new antibiotic for topical use. Antimicrob Agents Chemother. 1985;27:495–8. 10.1128/AAC.27.4.495. [PubMed: 3923922]

84•. Hetem DJ, Bootsma MCJ, Bonten MJM. Prevention of surgical site infections: decontamination with mupirocin based on preoperative screening for Staphylococcus aureus carriers or universal decontamination? Clin Infect Dis. 2016;62:631–6. 10.1093/cid/civ990. [PubMed: 26658054] One of two published mathematical models used to assess risk of mupirocin resistance associated with universal decolonization.

85. Coates T, Bax R, Coates A. Nasal decolonization of Staphylococcus aureus with mupirocin: strengths, weaknesses and future prospects. J Antimicrob Chemother. 2009;64:9–15. 10.1093/jac/dkp159. [PubMed: 19451132]

86. Hurdle JG. In vivo transfer of high-level mupirocin resistance from Staphylococcus epidermidis to methicillin-resistant Staphylococcus aureus associated with failure of mupirocin prophylaxis. J Antimicrob Chemother. 2005;56:1166–8. 10.1093/jac/dki387. [PubMed: 16275681]

87•. Deeny SR, Worby CJ, Tosas Auguet O, Cooper BS, Edgeworth J, Cookson B, et al. Impact of mupirocin resistance on the transmission and control of healthcare-associated MRSA. J Antimicrob Chemother. 2015;70:3366–78. 10.1093/jac/dkv249. [PubMed: 26338047] One of two published mathematical models used to assess risk of mupirocin resistance associated with universal decolonization.

88•. Septimus EJ, Schweizer ML. Decolonization in prevention of health care-associated infections. Clin Microbiol Rev. 2016;29: 201–22. 10.1128/CMR.00049-15. [PubMed: 26817630] A review of the current evidence for bacterial decolonization to prevent healthcare-associated infections.

89. Steed LL, Costello J, Lohia S, Jones T, Spannhake EW, Nguyen S. Reduction of nasal Staphylococcus aureus carriage in health care professionals by treatment with a nonantibiotic, alcohol-based nasal antiseptic. Am J Infect Control. 2014;42:841–6. 10.1016/j.ajic.2014.04.008. [PubMed: 24881497]

90. McConeghy KW, Mikolich DJ, LaPlante KL. Agents for the decolonization of methicillin-resistant Staphylococcus aureus. Pharmacotherapy. 2009;29:263–80. 10.1592/phco.29.3.263. [PubMed: 19249946]

91. Phillips M, Rosenberg A, Shopsin B, Cuff G, Skeete F, Foti A, et al. Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution. Infect Cont Hosp Epidemiol. 2014;35:826–32. 10.1086/676872.

92. Miedzybrodzki R, Fortuna W, Weber-Dabrowska B, Górski A. Phage therapy of staphylococcal infections (including MRSA) may be less expensive than antibiotic treatment. Postepy Hig Med Dosw (Online). 2007;61:461–5. [PubMed: 17679835]

93. Sikorska H, Smoragiewicz W. Role of probiotics in the prevention and treatment of meticillin-resistant Staphylococcus aureus infections. Int J Antimicrob Agent. 2013;42:475–81. 10.1016/j.ijantimicag.2013.08.003.

94. Alam F, Islam MA, Gan SH, Khalil MI. Honey: a potential therapeutic agent for managing diabetic wounds. Evid Based Complement Alternat Med. 2014;2014:169130–16. 10.1155/2014/169130. [PubMed: 25386217]

95. Fritz SA, Camins BC, Eisenstein KA, Fritz JM, Epplin EK, Burnham C-A, et al. Effectiveness of measures to eradicate Staphylococcus aureus carriage in patients with community-associated skin and soft-tissue infections: a randomized trial. Infect Control Hosp Epidemiol. 2011;32:872–80. 10.1086/661285. [PubMed: 21828967]

96. Rohr U, Mueller C, Wilhelm M, Muhr G, Gatermann S. Methicillin-resistant Staphylococcus aureus whole-body decolonization among hospitalized patients with variable site colonization by using mupirocin in combination with octenidine dihydrochloride. J Hosp Infect. 2003;54:305–9. 10.1016/S0195-6701(03)00140-3. [PubMed: 12919762]

97. Harris PNA, Le BD, Tambyah P, Hsu LY, Pada S, Archuleta S, et al. Antiseptic body washes for reducing the transmission of methicillin-resistant Staphylococcus aureus: a cluster crossover study. Open Forum Infect Dis. 2015;2:1–9. 10.1093/ofid/ofv051.

98. Parras F, Guerrero MC, Bouza E, Blázquez MJ, Moreno S, Menarguez MC, et al. Comparative study of mupirocin and oral co-trimoxazole plus topical fusidic acid in eradication of nasal carriage of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 1995;39:175–9. 10.1128/AAC.39.1.175. [PubMed: 7695302]

99. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52:e18–55. 10.1093/cid/ciq146. [PubMed: 21208910]

100. Malani PN. National burden of invasive methicillin-resistant Staphylococcus aureus infection. JAMA. 2014;311:1438–9. 10.1001/jama.2014.1666. [PubMed: 24715075]

101. Walker EM, Lowes JA. An investigation into in vitro methods for the detection of chlorhexidine resistance. J Hosp Infect. 1985;6: 389–97. 10.1016/0195-6701(85)90055-6. [PubMed: 2868036]

102. Morrissey I, Oggioni MR, Knight D, Curiao T, Coque T, Kalkanci A, et al. Evaluation of epidemiological cut-off values indicates that biocide resistant subpopulations are uncommon in natural isolates of clinically-relevant microorganisms. PLoS ONE. 2014;9: e86669 10.1371/journal.pone.0086669. [PubMed: 24466194]

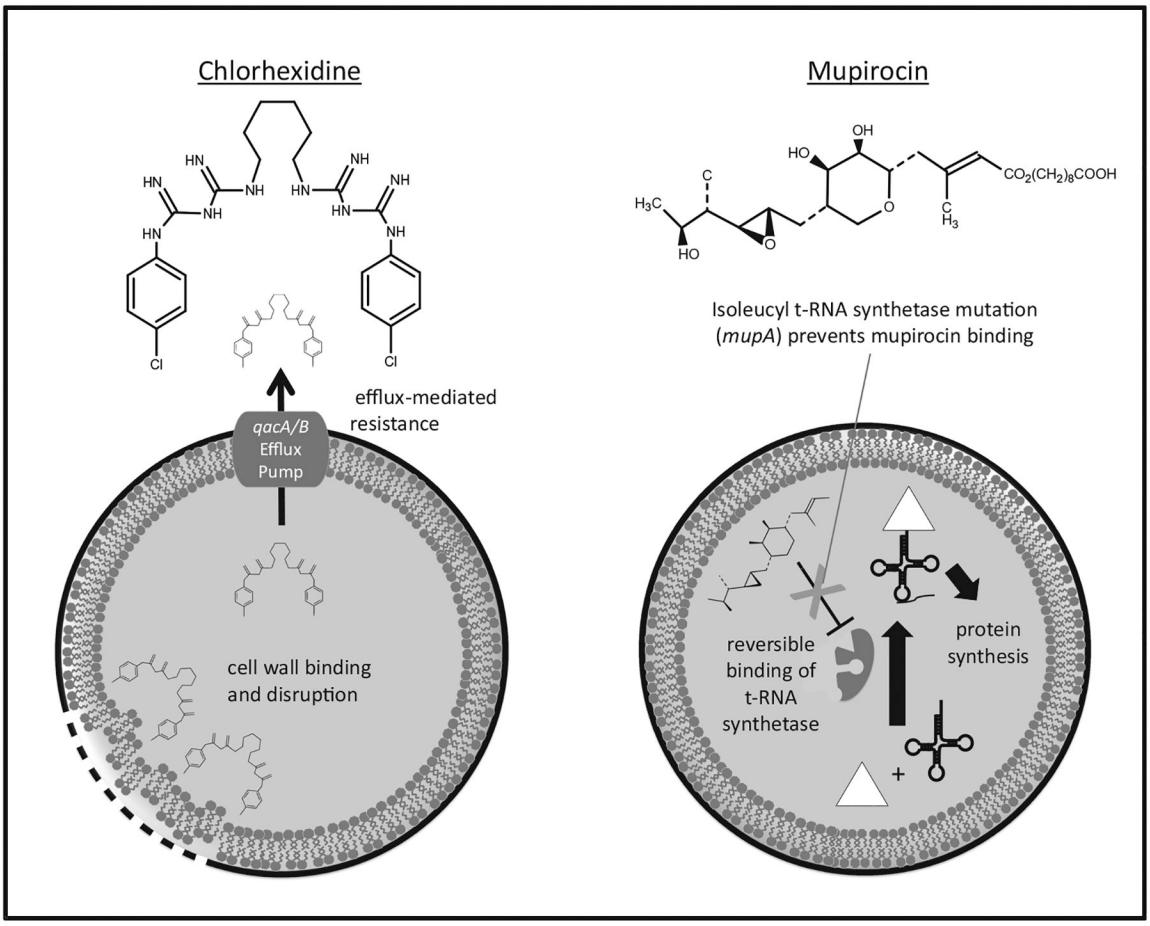

Fig. 1.

Mechanisms of bactericidal activity and resistance to CHG and mupirocin. *qacA/B* quaternary ammonium compound genes A and B, *t-RNA* transfer ribonucleic acid, *mupA* mupirocin resistance gene

Table 1

Summary of definitions, mechanisms, and prevalence of CHG resistance

Definitions	Mechanisms	Prevalence
Phenotypic: Measurement of bacterial susceptibility to CHG is problematic, and no standard methods for susceptibility testing exist; however, isolates with CHG MIC ≥ 4 μg/mL are generally recognized as resistant [34••]. Note. CHG diffuses poorly in agar and thus broth dilution method is preferred over disk diffusion [35]. Genotypic: As *qacA/B*-positive isolates typically have a CHG MIC ≥ 8 μg/mL [36], the presence of *qacA/B* has been used as a marker for CHG resistance [37]. However, *S. aureus* strains carrying *qacA/B* have been reported as CHG susceptible [32] and vice versa [38, 39].	Intrinsic resistance: Intrinsic CHG tolerance may be seen with non-enveloped viruses, certain non-fermenting gram-negative bacteria (e.g. *Pseudomonas* spp.), and mycobacteria [40]. Bacterial spores [25••] and biofilm formation [41] are also associated with reduced CHG effectiveness. Acquired resistance: *qacA/B* carriage is highly variable in different settings. The presence of *qacA/B* in staphylococci does not invariably confer phenotypic CHG resistance [42], and other *qac* genes (e.g., *smr, cepA, qacE)* [43] have also been associated with CHG resistance.	Prevalence of CHG resistance among *S. aureus* isolates ranges widely among healthcare settings, with increasing prevalence associated with higher levels of CHG use and clinical (versus surveillance) isolates, from 0.6% [34••] of the inpatient surveillance isolates, 0.9–1.6% [44,45] of the outpatient surveillance or clinical isolates, 17–33% [36, 46] of the ICU surveillance isolates, and up to 70% [47] of the clinical isolates (from Iranian hospitals with extensive CHG use). The prevalence of *qacA/B*-positive MRSA isolates has dramatically risen between 1990 and 2012 [48].

CHG chlorhexidine gluconate, *MIC* minimal inhibitory concentration, *qacA/B* quaternary ammonium compound genes A and B, *MRSA* methicillin-resistant *Staphylococcus aureus*

Table 2

Summary of definitions, mechanisms, and prevalence of mupirocin resistance

Definitions	Mechanisms	Prevalence
Susceptible: Susceptibility breakpoint of MIC ≤ 4 μg/mL has been described using agar and disk diffusion [59]. EUCAST defines MIC ≤ 1 μg/mL as susceptible and > 256 μg/mL as resistant (intermediate category described as undetermined significance) [60]. Low-level resistance: MIC 8–64 μg/mL occurs in staphylococci due to point mutations of the wild type *ileRS* gene (encoding isoleucyl t-RNA synthetase) [61•]. The clinical significance of low-level mupirocin resistance is not clear. *S. aureus* isolates with intermediate MICs between 128 and 256 μg/mL are uncommon [62•]. High-level resistance: CLSI defines only the presence or absence of high-level mupirocin resistance based upon broth microdilution (absent growth in 256-μg/mL well) or disk diffusion testing (absent zone of inhibition using 200-μg disk) [63••].	The plasmid-mediated *mupA* gene (also known as *ileS-2)* [62•] encodes a mutant isoleucyl t-RNA synthetase. *mupA* is ubiquitous among isolates examined with high-level mupirocin resistance [25••]. *mupA* is capable of transfer among bacteria via plasmids facilitated by insertion sequences. Isoleucyl t-RNA synthetase mutations may confer a fitness cost [64]. Although *mupA* is strongly associated with high-level mupirocin resistance, instances of low-level resistance are reported in the presence of *mupA* [25••].	A review of 11 studies (between 2001 and 2015) [25••] evaluating high level mupirocin resistance in MRSA noted prevalence ranging between 0% (in a neonatal intensive care unit that did not use mupirocin for decolonization) [65] to 9.4% (in a study of nursing home patients) [66]. Prevalence of high-level mupirocin resistance is notably lower among MSSA isolates, ranging between 0.3 and 1.2% [67, 68]. Epidemiologic studies suggest that mupirocin resistance is increasing overtime [51, 61•].

MIC minimal inhibitory concentration, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *t-RNA* transfer ribonucleic acid, *CLSI* Clinical Laboratory Standards Institute, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*