

Chlorhexidine: Expanding the Armamentarium for Infection Control and Prevention

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Health care–associated infections (HAIs) result in increased patient morbidity and utilization of health care resources. Rates of HAI are increasing despite advances in health care technology. Limited antimicrobial agents and a dry drug pipeline make novel prevention efforts critical. Chlorhexidine, an antiseptic solution that has been used worldwide since the 1950s, is a safe and effective product with broad antiseptic activity. Novel uses of chlorhexidine-containing products are being implemented to promote antisepsis and prevent bacterial colonization and infection. We review some of the many infection control applications of chlorhexidine in the battle against HAI, such as general skin cleansing, skin decolonization, preoperative showering and bathing, vascular catheter site preparation, impregnated catheter site dressings, impregnated catheters, and oral decontamination. As mandatory public reporting and pay for performance force infection control issues to the forefront, chlorhexidine-containing products may provide a vast armamentarium for the control and prevention of HAI.

Health care–associated infections (HAIs), the most common adverse events encountered by hospitalized patients [1], complicate the hospital course of up to 10% of people who are admitted to acute care hospitals. These often serious infections result in significantly increased patient morbidity, mortality, length of stay, and utilization of health care resources. As health care technology advances, ironically, so do rates of HAI. Novel uses of experienced products are being implemented to combat these challenging infections. Here, we review decades of experience with an increasingly popular antiseptic, chlorhexidine.

In this review, we focus on applications of chlorhexidine as an infection control tool to prevent HAI and present evidence for the use of chlorhexidine to decontaminate both people and devices (table 1). In addition, we address safety concerns, such as development of drug resistance and adverse drug reactions. Additional areas of needed research are addressed, highlighting high-risk populations that may benefit from chlorhexidine interventions but for whom data are currently lacking.

SPECTRUM OF ANTISEPTIC ACTIVITY AND ANTISEPTIC RESISTANCE

Chlorhexidine is a topical antiseptic solution that has been used worldwide since 1954. Its use in children and adults has provided an excellent record of safety and efficacy for applications as diverse as hand washing, preoperative skin preparation, vaginal antisepsis, treatment of gingivitis, and body washes to prevent neonatal sepsis. Chlorhexidine gluconate is a water-soluble, cationic biguanide that binds to the negatively charged bacterial cell wall, altering the bacterial cell osmotic equilibrium. Chlorhexidine is commercially available at a variety of concentrations (0.5%–4%) and formulations (with and without isopropyl alcohol or ethanol), and certain chlorhexidine-containing products are available over the counter. Because chlorhexidine-containing products come in many formulations and concentrations, we use “chlorhexidine” in this review to encompass chlorhexidine-containing solutions. At low concentrations, chlorhexidine affects membrane integrity, but at high concentrations, cytoplasmic contents precipitate, resulting in cell death [42, 43]. Chlorhexidine (0.05% solution) has broad activity against gram-positive and gram-negative bacteria, facultative anaerobes and aerobes, yeasts, and some lipid-enveloped viruses, including HIV [4, 44]. Chlorhexidine is not sporicidal.

Although decreased susceptibility to chlorhexidine has been reported, it has not been convincingly shown to be associated

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Table 1. Evidence supporting selected uses of chlorhexidine for infection control.

Application	Evidence in support of efficacy for specified chlorhexidine application ^a	Selected references
Antisepsis, skin		
Surgical hand scrub ^b	An 86%–92% reduction in hand skin flora (A)	[2, 3]
General skin cleansing ^b	Significant reduction in normal skin flora, gram-negative organisms, and <i>Staphylococcus aureus</i> (A)	[4, 5]
Daily bathing of ICU patients	Reduction of VRE acquisition rates in ICU patients (RR, 0.4) (B)	[6]
	Reduction of environmental VRE contamination (B)	[6]
	Reduction in acquisition of MRSA (32%) and VRE (30%) (B)	[7] ^c
	Decreased frequency of BSI (B)	[7, 8] ^c
<i>S. aureus</i> decolonization	Use of chlorhexidine plus mupirocin eradicated colonization in 69% of hemodialysis patients at 12 weeks (B)	[9]
	Use of chlorhexidine plus mupirocin, doxycycline, and rifampin eradicated MRSA colonization in 74% of patients at 3 months (B)	[10]
	Use of chlorhexidine plus mupirocin reduced the incidence of nosocomial <i>S. aureus</i> infection in the ICU by 66% over 4 years (B)	[11]
	Use of chlorhexidine plus mupirocin aids in outbreak control (A)	[12, 13]
Preoperative bathing	Significant reduction in skin microbial burden (A)	[14, 15]
	No clear evidence for reduction in SSI (C)	[16, 17]
Preoperative scrub ^b	Superior to other antiseptics in reducing skin flora at surgical site (A)	[18, 19]
	No clear evidence of reduction in SSI rate (C)	[17]
Central venous catheter site preparation ^b	50% Reduction in catheter colonization for chlorhexidine versus povidone-iodine (A)	[20]
	49% Reduction in catheter-related BSI comparing skin prep with chlorhexidine versus povidone-iodine (A)	[21]
Impregnated devices		
Vascular catheter dressings ^b	Reduction in catheter colonization (RR, 0.5–0.6) (A); no consistent reduction in BSI (C)	[22, ^c 23–25]
Epidural catheter dressings ^b	Reduction in catheter colonization (RR, 0.08–0.13) (A); no convincing data on reduction in catheter-related infections (C)	[26–29]
Vascular catheters	Reduction in catheter colonization (HR, 0.45) (A); reduction in catheter-related infections in high-risk groups (OR, 0.56) (B)	[30, 31]
Antisepsis, oropharynx		
Prevention of VAP	Reduction using random effects modeling (RR, 0.58–0.7) (B); clear benefit in cardiothoracic surgery patients. Overall benefit may relate to duration of mechanical ventilation. (B)	[32, 33]
Surgical site infection prevention	No evidence of an overall reduction in SSI rates (C); 36% reduction in deep SSI after elective cardiothoracic surgery (B)	[34]
Immunocompromised patients	No clear evidence of prevention or treatment of mucositis (C)	[35–37]
Antisepsis, other		
Burns	Use of chlorhexidine plus silver sulfadiazine reduced wound colonization with <i>S. aureus</i> (A); no clear evidence of reduction in secondary infections (C)	[38, 39]
Vaginal	No clear evidence of reduction in neonatal or maternal infections (C)	[40, 41]

NOTE. BSI, bloodstream infection; HR, hazard ratio; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; RR, relative risk; SSI, surgical site infection; VAP, ventilator-associated pneumonia; VRE, vancomycin-resistant enterococci.

^a A, strong evidence to support chlorhexidine efficacy; B, early evidence to support chlorhexidine efficacy; C, no consistent or clear evidence to support efficacy of chlorhexidine.

^b US Food and Drug Administration–approved indication. Safety data for most chlorhexidine-containing products have not been established for children aged <18 years, so most chlorhexidine-containing products have not been approved by the US Food and Drug Administration for children aged <18 years.

^c Data are from abstracts from national meetings of medical societies.

with repeated exposure to chlorhexidine. Proposed mechanisms include drug inactivation, efflux, and decreased uptake. Vancomycin-resistant enterococci (VRE) and vancomycin-susceptible enterococci, for example, have equivalent susceptibilities to chlorhexidine [45]. Some *Pseudomonas* species and other nonfermenting Gram-negative organisms have high-level resistance to chlorhexidine [46]. Plasmid-mediated resistance mechanisms to antiseptics are documented for staphylococci,

as are increased MICs [43]; however, the clinical significance of these increased MICs has not been determined, because they are usually far less than the commonly used chlorhexidine concentrations. Decreased susceptibility and the potential for emergence of resistance exist. Several laboratory studies have raised concerns that emergence of biocide nonsusceptibility may result in cross-resistance to antibiotics, but data are limited [47]. As antiseptics become used more broadly, surveillance of clinical

isolates should be considered to identify an epidemiologically significant trend toward decreasing antiseptic and antibiotic susceptibility.

SKIN ANTISEPSIS

General skin cleansing. Hand washing and skin antisepsis are now considered the most important interventions to prevent the spread of pathogens in hospitals. Use of chlorhexidine-based soaps and scrubs is supported by 25 years of clinical experience. Chlorhexidine rapidly reduces both skin flora and transient bacteria, such as Gram-negative bacteria. In the 1970s, hand washing with chlorhexidine was shown to reduce skin flora by 86%–92% [2, 3]. In addition, chlorhexidine has residual activity on the skin that helps to prevent rapid regrowth of skin organisms and enhances the duration of skin antisepsis. When surgeons used chlorhexidine hand scrubs, not only was there a greater reduction in the numbers of bacteria on the skin, compared with use of other antiseptic agents, but the bacterial count suppression was also maintained for up to 6 h [18, 48].

The spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and other multidrug-resistant organisms in hospitals has become a major infection prevention and control focus, especially as community-associated MRSA strains have emerged as a cause of HAI. MRSA is known to colonize the skin and can be detected by skin culture in 8% of healthy adults [49] and 8%–44% of patients admitted to the intensive care unit (ICU) [50, 51]. MRSA, like other hospital-acquired, multidrug-resistant organisms, is presumed to be transmitted from patient to patient in the ICU on the hands of health care workers. Historically, most infection control measures have focused on asepsis of health care providers and the environment. Increasingly, however, decolonization and decontamination of colonized patients is being evaluated.

Colonization with MRSA in adult ICU patients is known to increase the likelihood of subsequent MRSA infection [52]. Whether decolonization is an effective intervention to prevent subsequent infection remains to be shown, and current Centers for Disease Control and Prevention (CDC) guidelines do not recommend routine decolonization as a standard infection prevention intervention [53]. However, decolonization is often considered for hospitalized patients in units with high colonization pressure, a known risk factor for MRSA transmission in hospitals [54]. Whole-body washing with chlorhexidine can reduce skin colonization [5], but eradication of *S. aureus* colonization has been achieved only in combination with nasal mupirocin [9], and the addition of doxycycline and rifampin may enhance decolonization efforts in hospitalized patients [10]. Chlorhexidine has been used to control outbreaks of *S. aureus* infection [12, 13]. Several investigators have used chlorhexidine and intranasal mupirocin to effectively decolonize

MRSA carriers in ICUs with a high MRSA prevalence [55, 56]. The combination of intranasal mupirocin and chlorhexidine baths has been shown to reduce the incidence of nosocomial MRSA infection among ICU patients [11].

Whether chlorhexidine baths alone can reduce MRSA infection remains unknown. However, recent evidence suggests that decontaminating ICU patients with daily chlorhexidine baths may reduce transmission of other multidrug-resistant organisms and prevent HAI. Daily bathing of ICU patients with chlorhexidine decreased skin and environmental contamination with VRE and reduced the incidence of VRE acquisition (risk ratio [RR], 0.4; 95% CI, 0.1–0.9) in a comparison of the intervention period with 2 periods of bathing involving baths that did not contain chlorhexidine [6]. Not only did the intervention lead to decreased colonization of VRE on the skin of patients, but also fewer health care workers' hands were contaminated with VRE. Evidence is mounting that daily bathing of ICU patients with chlorhexidine may also reduce HAI. A recent multicenter study evaluated daily bathing of adult ICU patients with chlorhexidine and found a 32% decrease in the acquisition of MRSA colonization ($P < .05$), a surrogate for health care–associated transmission of MRSA. VRE acquisition decreased by 30% ($P < .01$), and the incidence of all bloodstream infections (BSIs) decreased by 21% ($P < .05$) [7]. This study evaluated a before-and-after intervention, and additional studies will be needed to confirm these promising results. Although there is growing literature evaluating the use of chlorhexidine baths for patients with recurrent MRSA abscesses and other infections with community-associated MRSA strains, further research is needed in this important area.

Preoperative bathing and surgical site preparation.

Early studies demonstrated the utility of chlorhexidine-based soaps and hand scrubs; a natural extension of use of this agent lies in the field of preoperative baths and skin preparation for surgical patients. Postoperative surgical site infections (SSIs) are frequently caused by a patient's own skin flora, including those microorganisms that colonize body sites other than the surgical site. Similar to hand washing with chlorhexidine, chlorhexidine whole-body bathing significantly reduces microbial burden on the skin [14], and repeated baths lead to a progressive reduction of organisms over time [15]. Preoperative bathing and scrubbing with chlorhexidine is superior to preoperative bathing and scrubbing with povidone-iodine in reducing skin colonization at the site of surgical incision [57]. Preoperative baths are widely encouraged in clinical practice. Although we expect that decreasing general skin contamination in preoperative patients will decrease the number of SSIs, a clear cause-and-effect relationship has not been established to date. A recent Cochrane systematic review identified randomized, controlled trials of full-body bathing or showering with chlorhexidine, compared with placebo or regular soap, and

found no clear evidence that preoperative bathing with chlorhexidine was more effective at reducing surgical site infections [16, 17]. Some of these studies entailed full-body rinsing after application of chlorhexidine, and this may have impacted chlorhexidine's antiseptic activity, so conclusions about preoperative bathing should be interpreted with caution.

Chlorhexidine- and iodine-containing compounds are frequently used to prepare the skin immediately before surgery because of both agents' utility in reducing skin microorganisms. After a single application, chlorhexidine achieves greater reduction in skin flora and has longer residual activity than does povidone-iodine [18, 19]. Chlorhexidine, unlike the iodophors, is active even in the presence of blood or serum proteins. There is extensive data demonstrating the reduction in skin flora resulting from use of these products, but again, there is no clear comparison demonstrating superiority of either of these products in reducing SSIs [4]. The benefits of chlorhexidine skin preparation are more evident when used in preparation for central venous catheter (CVC) insertion.

INSERTION AND MAINTENANCE OF DEVICES

Intravascular catheters are an integral component of 21st century medical care. The advantages of prolonged and secure venous access are counterbalanced by the added risks of infectious and noninfectious complications. Historically, in the United States, povidone-iodine has been used to prepare the skin for CVC insertion [58]. Current data, however, support chlorhexidine as the preferred agent for skin preparation before CVC placement.

The exact mechanism by which chlorhexidine reduces BSIs is unknown. For short-term catheters, skin organisms that colonize the catheter site are postulated to migrate along the catheter insertion tract and contaminate the catheter tip [59]. A multicenter study of neonates showed that skin preparation for peripheral intravenous catheter insertion with chlorhexidine reduced catheter colonization by 50%, compared with use of povidone-iodine [20]. This reduction of catheter colonization is postulated to decreased likelihood of developing a catheter-related BSI. In 1991, Maki et al. [60] reported that preparation of the CVC insertion site with chlorhexidine decreased BSI rates, compared with preparation with 70% alcohol or 10% povidone-iodine. In 2002, a meta-analysis reviewed 8 studies (involving 4143 catheters) found a 49% rate of reduction (RR, 0.51; 95% CI, 0.27–0.97) in the risk of catheter-related BSIs among patients whose skin was prepared with chlorhexidine [21]. The 2002 CDC's "Guidelines for the Prevention of Intravascular Catheter-Related Infections" recognized the data supporting use of chlorhexidine for CVC placement and recommended a chlorhexidine-based preparation over tincture of iodine, an iodophor, or 70% alcohol for cutaneous antisepsis before CVC placement [61].

Chlorhexidine products are also used in the maintenance of indwelling catheters in attempts to prevent infectious complications. Catheter site colonization is postulated as the main portal of entry for bacteria that travel down the insertion tract and colonize the catheter tip [59]. To suppress microorganisms around the catheter insertion site, chlorhexidine-impregnated sponges are available that can be placed circumferentially around the catheter. Early studies compared these sustained-release chlorhexidine dressings with a transparent dressing in 2 university hospital ICUs. The treatment group had a reduced risk of catheter colonization (RR, 0.62; 95% CI, 0.49–0.78) and a lower rate of catheter-associated BSIs (RR 0.38; 95% CI, 0.16–0.89) [22], but these data remain unpublished. A multicenter trial involving 6 neonatal ICUs evaluated the impact of chlorhexidine-impregnated dressings on BSI rates and catheter colonization [23]; the study revealed that the neonates randomized to receive chlorhexidine-impregnated dressings were less likely to have colonized central catheter tips, compared with neonates whose catheter site care involved either povidone-iodine or 70% alcohol; however, both groups were equally likely to have a BSI (RR, 1.1; 95% CI, 0.8–1.5). A study of children who had undergone cardiac surgery revealed a significant reduction in catheter colonization among patients whose CVCs were maintained with a chlorhexidine-impregnated dressing, but again, there was no difference in the rates of BSIs [24]. The CDC's "Guidelines for the Prevention of Intravascular Catheter-Related Infections" from 2002 made no recommendations regarding the use of chlorhexidine-impregnated dressings to reduce incidence of infection [61]. Although these data consistently find decreased colonization of CVCs, few published data demonstrate decreases in catheter-associated BSIs to support widespread use of chlorhexidine-impregnated dressing use. This is a promising area for further research.

Catheters and catheter cuffs can be impregnated or coated with antiseptics or antimicrobial agents. Coating of catheters with chlorhexidine in combination with silver sulfadiazine has been studied as a novel method to reduce catheter-associated BSIs. A meta-analysis from 1999 of randomized trials in which chlorhexidine- and silver sulfadiazine-impregnated CVCs were compared with nonimpregnated catheters revealed that use of catheters impregnated on the external lumen reduced the incidence of both catheter colonization and catheter-associated BSI [30]. A study of second-generation chlorhexidine- and silver sulfadiazine-impregnated CVCs, with coating on both the intra- and extraluminal sides, found decreased rates of catheter colonization, compared with the rates for standard catheters [31]. This study was not able to demonstrate a reduction in the number of catheter-associated BSIs, because it was underpowered. Chlorhexidine- and silver sulfadiazine-impregnated catheters are significantly more expensive than standard catheters; therefore, they are currently cost-effective only for select

patient populations for whom BSI rates are high despite the use of appropriate infection control practices and insertion techniques [62]. The cumulative evidence regarding the efficacy of antiseptic-impregnated catheters in decreasing the rate of catheter-associated BSI is promising for high-risk patients, but other infection control interventions may be more cost-effective in areas with low rates of BSI and for low-risk patients.

DECONTAMINATION OF THE OROPHARYNX

In addition to skin cleansing, chlorhexidine is increasingly being evaluated for decontamination of the oropharynx. Chlorhexidine products effectively decontaminate the oropharynx and have been used for decades by dentists for controlling gingivitis and periodontitis. The applications of chlorhexidine in controlling oral infections is beyond the scope of this review, but we will point out that studies that have evaluated oral chlorhexidine rinses to decrease oral flora and prevent oral complications in bone marrow transplant recipients and other patients with malignancies have yielded mixed results [35, 36, 63].

Ventilator-associated pneumonia is a major cause of morbidity and mortality in patients hospitalized in intensive care units. Periodontal disease and poor oral hygiene have been correlated with nosocomial pneumonia [64]. Several investigators have studied the impact of chlorhexidine decontamination of the nasopharynx and oropharynx on prevention of HAI. These studies have yielded mixed results: some have shown a reduction in the incidence of ventilator-associated pneumonia [65], and others have shown no impact on rates of ventilator-associated pneumonia [66]. Segers et al. [34] specifically studied the incidence of HAI among patients undergoing elective cardiothoracic surgery. In this population, the authors found that perioperative decontamination of the oropharynx and nasopharynx with chlorhexidine was effective at reducing the absolute risk of postoperative HAI (risk reduction, 6.4%; 95% CI, 1.1%–11.7%). Patients in the treatment group had fewer lower respiratory tract infections and deep SSIs, but there was no significant reduction noted for the overall rate of SSI. A recent meta-analysis concluded from the available literature that, overall, chlorhexidine decontamination may reduce the incidence of ventilator-associated pneumonia by 30% [32]. The authors note that the benefits may be most significant for cardiac surgery patients undergoing coronary bypass grafting when the duration of postoperative intubation is shorter. The practice of oral decontamination for perioperative patients and ICU patients undergoing ventilation is highly variable. Questions still remain about cost-effectiveness, long-term safety, and the generalizability of the efficacy reported in the aforementioned studies.

SAFETY

For decades, chlorhexidine has been a well-tolerated, broadly used, skin and mucous membrane disinfectant. The most frequent adverse reaction to chlorhexidine is contact dermatitis (table 2), but rare cases of hypersensitivity and anaphylaxis have been reported [68]. Contact of chlorhexidine with the inner ear may result in permanent hearing loss [69]. In a rat model, direct application of chlorhexidine on neural tissue caused a dose-dependent degeneration of adrenergic nerves [71]. As a result, chlorhexidine for skin preparation before use of epidural catheters has not been routinely adopted for fear of damage to neural tissue; however, there are no clinical data to discourage the use of chlorhexidine for skin preparation before lumbar puncture, epidural catheter placement, or neurosurgical procedures.

Chlorhexidine is poorly absorbed through intact adult skin [72]. Since the 1970s, investigators have studied the efficacy of wiping or bathing neonates with chlorhexidine to reduce neonatal sepsis, and no significant adverse events have been reported [73–78]. A recent, comprehensive review concluded that some percutaneous absorption occurs at trace levels, particularly in preterm infants [79]; however, there have been no reports of adverse consequences as a result of chlorhexidine absorption in pediatric patients and no data to suggest that trace levels have clinical importance. Safety data for most chlorhexidine products have not been established in children (age, <18 years), so most chlorhexidine products have not been approved by the US Food and Drug Administration for such children. To our knowledge, no chlorhexidine product has been approved for children aged <7 years.

CONCLUSIONS

Historically, most infection prevention and control measures have focused on asepsis of health care providers and the environment. Emerging evidence for the role of host decontamination in preventing HAI is changing the paradigm and paving a new path for novel infection prevention interventions. Chlorhexidine has a long-standing track record of being a safe and effective product with broad antiseptic activity and little evidence of emerging resistance. As the limelight is directed toward

Table 2. Known adverse effects of chlorhexidine.

Adverse effect	Frequency	Reference
Dermatitis	Rare	[67]
Hypersensitivity reaction and anaphylaxis	Case reports ^a	[68]
Ototoxicity	Case report	[69]
Corneal injury	Case report	[70]

^a Anaphylaxis after topical application and impregnated catheter insertion.

control and prevention of HAIs, chlorhexidine-containing products may provide a vast tool kit for infection control practitioners. Increasing rates of multidrug-resistant bacteria, including MRSA and VRE, demand evidence-based research of novel interventions to prevent transmission of multidrug-resistant organisms and HAI. A delicate balance must be achieved between the rigorous regulatory oversight inherent in the traditional research model and the necessity for innovative quality-improvement initiatives, such that novel products can be tested in high-risk populations, including children. Given the promising preliminary studies discussed above, further research is essential to support evidence-based recommendations for the use of many chlorhexidine products in infection control and prevention.

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