American Journal of Infection Control 41 (2013) S49-S55

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Original research article

Reducing the risk of surgical site infections: Does chlorhexidine gluconate provide a risk reduction benefit?

Charles E. Edmiston, Jr. PhD [a,*], Benjamin Bruden PharmD [b], Maria C. Rucinski BS [c], Cindy Henen RPh [b], Mary Beth Graham MD [d], Brian L. Lewis MD [a]

[a] Department of Surgery, Medical College of Wisconsin, Milwaukee, WI
[b] Pharmacy Department, Froedtert Hospital, Milwaukee, WI
[c] Florida State University School of Medicine, Tallahassee, FL
[d] Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

Key Words:
Surgical site infection
Chlorhexidine gluconate
Wound irrigation
Preadmission showering/cleansing
Skin antisepsis

Chlorhexidine gluconate (CHG) has been available as a topical antiseptic for over 50 years, having broad clinical application throughout the health care environment. Evidence-based clinical studies have shown chlorhexidine gluconate to be a safe and effective perioperative skin-prepping agent. Renewed interest has emerged for use of the antiseptic bath/shower to reduce the microbial skin burden prior to hospital admission. Recent clinical studies have documented that multiple applications of 2% or 4% CHG using a standardized protocol results in high skin surface concentrations sufficient to inhibit/kill skin colonizing flora, including methicillin-resistant *Staphylococcus aureus*. A new focus for the use of CHG in surgical patients involves irrigation of the wound prior to closure with 0.05% CHG followed by saline rinse. Recent laboratory studies suggest that, following a 1-minute exposure, 0.05% CHG produces a >5-log reduction against selective health care-associated pathogens and reduces microbial adherence to the surface of implantable biomedical devices. General, orthopedic, cardiothoracic, and obstetrical surgical studies have documented the safety of selective CHG formulations in elective surgical procedures. The following discussion will address both the evidence-based literature and preliminary findings suggesting that CHG has a broad and safe range of applications when used as an adjunctive interventional strategy for reducing the risk of postoperative surgical site infections (SSI).

Chlorhexidine gluconate (CHG) has been an important component in our efforts to reduce the risk of health care-associated infections. It has been available as a topical antiseptic agent for more than 50 years and is viewed as a safe and efficacious agent, encompassing a wide spectrum of clinical applications.[1-8] CHG exhibits a broad-spectrum of activity that includes gram-positive, gram-negative nonspore-forming bacteria, yeast, and selective lipid envelope viruses, including HIV.[6,7,9] The mechanism of action of CHG is variable and is highly dependent on skin surface concentration. The antimicrobial activity is due in part to the binding of the CHG cationic molecules to the negatively charged components of the bacterial cell wall. At low concentrations, the agent exerts a bacteriostatic effect by causing an alteration of the bacterial cell osmotic equilibrium resulting in leakage of potassium and phosphorus, inhibiting growth. At high concentrations, the agent is rapidly bactericidal, the result of precipitation of the bacterial cell cytoplasmic contents.[10,11]

The effectiveness and widespread use of CHG has led to some concern over the emergence of bacterial resistance. A study published in 1999 involving over 1,100 gram-positive and gram-negative clinical isolates, including strains of multidrug-resistant microorganisms found a low incidence of CHG resistance against clinically significant microbial populations. No isolates in this study exhibited high-level CHG resistance.[12] In a study conducted in Taiwan over a 15-year period (1990-2005), the investigators noted a 2-dilution shift (increase) in the minimum inhibitory concentration $(MIC)_{90}$ of selective clinical isolates.[13] A recent interesting observation from Hong Kong found that a quaternary ammonium compound (*qac*) gene, encoding for efflux proteins present in selected staphylococcal strains, was found in greater

* Address correspondence to Charles E. Edmiston, Jr., PhD, Department of Surgery, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.
E-mail address: edmiston@mcw.edu (C.E. Edmiston).

Publication of this article was supported by Advanced Sterilization Products (ASP).
Conflicts of interest: None to report.

http://dx.doi.org/10.1016/j.ajic.2012.10.030

frequency among selective health care workers (nurses) than the general public. These colonizing staphylococcal isolates had a reduced susceptibility to benzalkonium chloride and CHG compared with gene-negative islolates.[14] Furthermore, it has been suggested that subinhibitory biocide exposure under experimental laboratory conditions will induce *qac* gene expression.[15] Therefore, there exists a theoretical possibility that exposure to biocides such as CHG could exert a selective pressure on antibiotic-resistant strains, facilitating their survival within the health care environment. However, it is important to note that a "reduced susceptibility" to CHG does not necessarily translate into diminished antimicrobial effectiveness when the biocide is used at the appropriate (application) concentration. Further surveillance studies are warranted, documenting future changes in the antiseptic activity of CHG against clinically relevant microbial populations.

MAKING THE CLINICAL CASE FOR CHG IN THE SURGICAL PATIENT POPULATION

Preadmission skin antisepsis

The concept of the preadmission shower as a risk reduction strategy was addressed in the 1999 Centers for Disease Control and Prevention Hospital Infection Control Practices Advisory Committee document, *Guideline for the Prevention of Surgical Site Infection*.[16]

> "A preoperative antiseptic shower or bath decreases skin microbial colony counts. In a study of >700 patients who received two preoperative antiseptic showers, chlorhexidine reduced bacterial colony counts nine-fold (2.3×10^2 to 0.3), while povidone-iodine or triclocarban-medicated soap reduced colony counts by 1.3- and 1.9-fold, respectively."

This process was designated by the Centers for Disease Control and Prevention guidelines as a category 1B clinical practice and is "strongly recommended." Whereas there is universal agreement that a 2% or 4% CHG whole-body bath or shower will reduce bacterial colonization of the skin, there was no definitive data to suggest that this practice was an effective strategy for reducing postoperative surgical site infections.[16,17] The Cochrane Collaborative review published in 2007 reviewed 9 clinical trials from 1983 to 2005 and suggested that existing evidence-based data did not justify continuation of this practice.[18] A recent meta-analysis evaluated 16 clinical trials from 1979 to 2011, involving a total of 9,980 patients, came to a similar conclusion that whole-body showering or cleansing showed no benefit in preventing postoperative surgical site infection.[19] A separate analysis published in 2011 found that many of the previous clinical studies were technically and scientifically flawed and that a rigorous standardization was lacking.[20] Whereas most analyses appear not to support the routine use of the preadmission whole-body cleansing or showering, several factors should be considered when evaluating this low risk and low cost intervention:

- CHG surface skin concentrations accumulate with repetitive application, and, therefore, single application may not approach concentrations sufficient to inhibit skin flora.
- Standardization is an important component of any antiseptic body cleansing or showering process; previous studies have failed to validate this aspect of the practice.
- A discussion of measuring patient compliance is often excluded from most published protocols.

In an effort to address the impact of protocol standardization and repetitive application on skin surface concentrations of CHG, a randomized, prospective study was conducted in the Department of Surgery at the Medical College of Wisconsin comparing the application of 4% CHG aqueous soap to 2% CHG-impregnated polyester cloths. Several variables were considered: (1) number of applications, (2) timing of the applications, (3) CHG application at multiple body sites, and (4) specific application instructions provided to the participants (patients). Volunteers were randomized into 3 groups: (1) showering or cleansing once in the evening; (2) showering or cleansing once in the morning; and (3) showering or cleansing twice, in the evening and morning. In an exploratory pilot study, individuals were given 4% CHG without any specific instructions except they were told to shower once in the evening, once in the morning, or twice (evening and morning). In this nonstandardized process, the skin surface concentrations of CHG as measured at 5 separate anatomic sites were often below the MIC_{90} concentration require to inhibit or kill staphylococcal skin isolates. However, when specific and detailed timed application instructions (standardized) were provided to the volunteers (patients), even a single shower (4%) or cleansing (2%) resulted in CHG skin surface concentrations well above that required to inhibit or kill staphylococcal microbial populations. The highest skin surface concentrations were observed when 2 showers or cleansings were implemented. The ratio of C_{CHG}/MIC_{90} ranged from 25.3 for the 4% formulation to 349.1 for the 2% CHG-impregnated cloths.[21]

Several recent reports using a standardized process have documented the benefit of preadmission skin antisepsis. In an orthopedic population undergoing total joint replacement, the preinterventional infection rate was 3.19% (N = 727), whereas, in a postinterventional population where patients were instructed to cleanse the night before and once again in the hospital ambulatory area prior to surgery using the 2% CHG-impregnated cloths, the infections rate was 1.59% (N = 424).[22] A second study (quality initiative) in total hip and knee replacement, gastric bypass, C-section, and bone fusion patients (N = 5,570), using a bundled approach of a standardized active methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance and presurgical antisepsis protocol (application of 2% CHG-impregnated wipes, once prior to surgery), documented a significant reduction ($P < .019$) in surgical site infection postimplementation (0.57%, N = 7/1,225) compared with the preinterventional period (1.55%, N = 17/1,094).[23] A third study in an orthopedic patients population using a bundling strategy of active surveillance for methicillin-susceptible *Staphylococcus aureus*/MRSA, decolonization in all positive patients (nasal mupirocin, twice daily for 5 days), and total body wash with 4% CHG aqueous (5 days) found a significant reduction in the rate of selective MRSA infections ($P < .032$) and total surgical site infections (SSI) ($P < .0093$) during the intervention period (N = 7,019) compared with a control period (N = 5,293).[24]

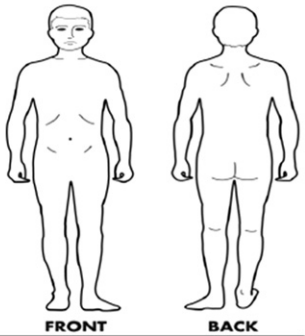
An unresolved question regarding the preadmission application of CHG is what is the optimal number of applications prior to surgery? Because skin surface activity is enhanced following multiple applications of CHG, most practitioners are recommending 2 to 5 separate application prior to surgery. Each patient undergoing an elective surgical procedure at Froedtert Hospital in Milwaukee, Wisconsin, is given an instruction sheet (Fig 1) describing the preadmission body cleansing process using a 2% CHG-impregnated polyester cloth. Those instructions recommend a minimum of 2 applications prior to admission (night before and morning of surgery). This information is also conveyed orally to the patient when she or he undergoes preoperative testing. The instructional sheet serves as a reinforcement and point of reference for the patient. Compliance is of course a significant component of any successful patient-directed interventional strategy. A recent study conducted in an orthopedic patient population undergoing total joint or spine surgery looked at compliance rates for preoperative use of CHG total body washing and intranasal mupirocin

Preparing the Skin Before Surgery

Preparing or "prepping" skin before surgery can reduce the risk of infection at the surgical site. To make the process easier, this facility has chosen disposable cloths moistened with a no-rinse, 2% Chlorhexidine Gluconate (CHG) antiseptic solution. The steps below outline the prepping process and should be carefully followed.

Night Before Surgery:

- Shower the night before surgery at least 1 hour before you prep your skin for the first time
- Do not allow this product get into your eyes, ears, and mouth
- Prep the skin as directed using 1st package of cloths
- Stop use if redness or irritation occurs
- Do not apply lotions, moisturizers or makeup after prepping
- Dress in clean clothes/sleepwear
- Remove the sticker from used package and apply to this form.



How to Use Cloths:

1. Prep only the circled areas above
2. Scrub the skin back and forth for 3 minutes with 1 cloth
3. Do not rinse
4. Allow to air dry
5. Discard each cloth after a single use
6. **Repeat** process with second cloth

Morning of Surgery:

- You may shower, wait 1 hour to prep skin
- Prep skin as directed using 2nd package of cloths
- Do not apply lotions, moisturizers or makeup after prepping
- Dress in clean clothes/sleepwear
- Remove the sticker from used package and apply to this form
- Bring this form with you to your surgery.

Fig 1. Patient instruction handout describing the preadmission body cleansing process using 2% chlorhexidine gluconate impregnated polyester cloths.

administration. Patients were required to purchase out-of-pocket both the CHG aqueous body wash and topical mupirocin from a local pharmacy. A total of 81% of patients followed the nasal decolonization regimen, and 89% followed the CHG body-washing regimen. Although patient compliance was viewed as relatively high, one barrier to compliance was ease of obtaining CHG and mupirocin, which was viewed as difficult by some patients.[25] Ideally, both CHG and, in the case of the decolonization regimen, mupirocin should be provided to the patient along with printed instructions in an effort to maximize the benefit and enhance compliance to the interventional bundle.

Current evidence-based studies would suggest that preadmission skin surface cleansing with CHG-impregnated polyester cloths or application of CHG to the skin as an aqueous solution would appear to have equal efficacy.[22-24] Similar findings have been noted in patients undergoing daily bathing/cleansing in the intensive care unit. A recent meta-analysis has documented that bathing with aqueous CHG or skin surface cleansing with CHG-impregnated cloths were equally effective ($P = .03$, $P < .006$, respectively) in reducing the incidences of health care-associated bloodstream infections.

CHG in perioperative skin antisepsis

Skin antisepsis is viewed as a fundamental component of the perioperative effort to reduce the risk of surgical site infections, and several antiseptic agents have been identified as beneficial to this process.[16] The iodophors, CHG, or an alcohol-containing derivative of both products are the most common agents used in surgery. Both the iodophors and chlorhexidine exhibit a broad spectrum of antimicrobial activity, but, as previous discussed, CHG demonstrates an accumulative or residual activity on the skin, and its activity does not appear to be influenced by blood or tissue proteins.[7] Does CHG offer a selective advantage as a skin-prepping agent for reducing the risk of surgical site infections? Most studies looking at CHG efficacy have focused on what would be viewed as "surrogate" studies, where SSI reducing is not the primary outcome but rather reduction of skin surface flora at the incision site. A study conducted in patients undergoing foot surgery was randomized to 1 of 3 skin-prepping groups; 3% parachlorometaxylenol (PCMX), 0.7% iodine + 74% isopropyl alcohol, or 2% CHG + 70% isopropyl alcohol. The study found that the CHG/alcohol combination resulted in a significant ($P < .001$) qualitative and quantitative reduction in foot flora (hallux and toes sites) compared with study comparators.[26] A second study compared 2% CHG + 70% isopropyl alcohol to 0.7% iodine + 74% isopropyl alcohol or 0.75% iodine scrub + 1% iodine paint in patients undergoing elective shoulder surgery. The authors found that the CHG/alcohol skin-prepping solution was superior to the other 2 agents ($P < .01$) in reducing staphylococcal skin surface flora from the incision site.[27] In a randomized clinical trial in patients undergoing vaginal hysterectomy ($N = 50$), the authors found that patients who were prepped with 4% CHG compared with 10% povidone-iodine demonstrated at 30 minutes a significant ($P < .003$) reduction in contaminating skin flora compared with the iodophor group.[28] This statistical benefit, however, did not persist at 90 minutes postapplication. A "surrogate" study published in 2012 compared the efficacy of 0.7% iodine + 74% isopropyl alcohol against 2% CHG + 70% alcohol in patients undergoing lumbar spine surgery. Both agents were equally effective in eradicating (quantitatively) flora overlying the lumbar spine.[29]

Surrogate studies, although helpful in delineating microbiologic efficacy, do not supplant the benefits of a rigorous clinical trial in assessing clinical efficacy. However, few studies have adequately assessed the comparative clinical advantage of one skin-prepping agent over another in a prospective, randomized clinical trial. At the University of Virginia, surgical investigators conducted a single institution, quasiexperimental study in general surgical patients (N = 3,209 operations) looking at clinical outcomes associated with 3 separate skin-prepping regimens using a sequential (6 month) implementation design: (regimen A) 10% povidone-iodine scrub combination with an isopropyl alcohol application between steps; (regimen B) 2% CHG + 70% isopropyl alcohol; and (regimen C) 0.7% iodine povacrylex + 74% isopropyl alcohol. Patients were followed for 30 days postoperatively as part of an ongoing American College of Surgeons National Quality Improvement Program initiative. The primary outcome was overall rate of SSIs by 6 months performed in an intent-to-treat manner. The results were highly provocative with the lowest infection rate observed in regimen C, 3.9%, compared with 7.1% for regimen B ($P < .002$). Subgroup analysis documented no difference in outcomes between patients prepped with povidone-iodine scrub-paint or prepped with iodine povacrylex in isopropyl alcohol; these patients had significantly lower surgical site infection rate compared with patients prepped in the 2% CHG and 70% isopropyl alcohol (4.8% vs 8.2%, respectively; $P < .001$) group.[30] In a separate multicenter, prospective, randomized clinical trial comparing 10% povidone-iodine (N = 409) with 2% CHG + 70% isopropyl alcohol (N = 440) in clean-contaminated surgical cases, investigators found that the overall rate of SSI was significantly lower in the CHG/alcohol group compared with povidone-iodine group (9.5% vs 16.1%, respectively, $P < .004$). The CHG/alcohol combination was superior to the povidone-iodine group in reducing the risk of both superficial incisional (4.2% vs 8.6%, respectively, $P < .008$) and deep incisional (1% vs 3%, respectively, $P = .05$) surgical site infections.[31] Whereas these 2 clinical trials present conflicting results, from an evidence-based perspective, the latter (Darouiche et al[31]) study is viewed as methodologically superior. However, it should be pointed out that the Darouiche et al study is also perceived as flawed because the CHG/alcohol skin-prepping agent was not compared against an alcohol/iodine comparator. It should, however, be noted that this study is the first clinical trial to document the benefit of a selective skin-prepping agent (2% CHG/70% isopropyl alcohol) to significantly reduce the risk of superficial and/or deep incisional surgical site infections in clean-contaminated surgical procedures.

In 2010, a meta-analysis of 7 randomized clinical trials (N = 3,614 patients) was published comparing CHG (0.5%-4%) with iodine (0.7%-10%) for preoperative skin antisepsis as an effective risk reduction strategy for preventing surgical site infections. The analysis noted that use of CHG was associated with fewer surgical site infections (adjusted risk ratio, 0.64; 95% confidence interval: 0.51-0.80) compared with iodine. In a cost benefit model, sensitivity analysis documented that switching from iodine to CHG resulted in a net savings per surgical case of $16 to $24, projecting a yearly saving of $349,904 to $568,594 per year for the collective surgical services.[32] The myriad of "surrogate" and clinical studies suggest that a CHG + alcohol combination would appear to be the most effect skin antiseptic agent for reducing the risk of surgical site infections. The addition of an alcohol base lends an enhanced component to the broad-spectrum activity of CHG, further augmented by documented residual activity of CHG on the surface of the skin.[6,7,16,17] One cautionary comment: any skin antiseptic agent containing alcohol, including CHG must be allowed to dry prior to draping so as to reduce the likelihood of a fire occurring during electrocautery.

Intraoperative irrigation: Does CHG have a role in reducing risk?

The view that "the solution to pollution is dilution" has been the driving force behind the widespread application of intraoperative irrigation across the spectrum of surgical services.[33] The combination of saline irrigation and debridement plays a major role in the management of traumatic open fractures in orthopedic surgery.[34] Intraoperative (saline) lavage has been a long-standing tradition in general surgery, especially following spillage of fecal contents after penetrating trauma or intraoperative injury.[35,36] However, the addition of antimicrobial agents to the intraoperative lavage fluid has been viewed within selective surgical disciplines as an important strategy for reducing postoperative infection. Unfortunately, in an era of evidence-based medicine, it is difficult to assess the clinical efficacy in light of the paucity of well-designed randomized, controlled clinical trials. Therefore, in the absence of established clinical guidelines, the scientific merit of this practice remains purely within the realm of dogmatism.

The process of augmenting irrigation fluids with additives agents such as antimicrobials has been a continuous source of controversy in surgery. An experimental study published in 1990 noted that, following penetrating bowel injury, there is a rapid contamination of the serosal mesothelium by both gram-positive and gram-negative fecal populations, stimulating an intense inflammatory response (Fig 2A). A copious saline lavage was highly effective (5- to 6-log reduction) at removing "free particulate" contamination from the peritoneal cavity. However, peritoneal lavage, even with the addition of selective antibiotics (cephazolin, kanamycin, and/or metronidazole), was ineffective at reducing peritoneal mesothelial contamination.[33] Mechanistically, most antimicrobials agents are effective against microorganisms when drug exposure occurs during their logarithmic growth phase. Therefore, the process of antibiotic-lavage or irrigation does not realistically afford sufficient contact time to efficiently kill or inhibit bacterial growth within the peritoneal cavity. In addition to the question of clinical efficacy, selective case reports have suggested that local antimicrobial irrigation may be associated with severe intraoperative anaphylaxis, which has been seen with bacitracin irrigation during selective surgical procedures (cardiac, orthopedic, general, and neurosurgical).[37] In a study published in 2003, investigators attempted to retrospectively evaluate the benefits of antibiotic (neomycin/bactracin) irrigation versus normal saline following pacemaker insertion (N = 418), coronary artery bypass procedures (N = 1,464), and laminectomy (N = 941). A total of 2,823 surgical procedures was evaluated: 1,043 irrigated with an antibiotic, and 1,780 used normal saline. There was no significant difference in the surgical wound infection rate between those patients irrigated with antibiotic solution versus normal saline.[38] A retrospective analysis of 176 consecutive appendectomies found that intraoperative saline irrigation in open versus laparoscopic appendectomy did not prevent intra-abdominal abscess formation.[39] A recent retrospective study involving 1,063 surgical appendectomy cases suggested that abdominal irrigation with an imipenem (N = 194) solution was superior ($P < .05$) to irrigation with normal saline (N = 661) or Dakin's solution (N = 208) in cases of appendicitis.[40] However, the breakdown of parenteral administration of antibiotics per irrigation group was not disclosed in this paper, therefore making it difficult to assess the actual efficacy of the antimicrobial irrigation solution. Some recent papers in the orthopedic literature suggest that, even in selective contaminated (infected) cases, antibiotic irrigation is unlikely to have a significant impact on improving clinical outcome.[34,41]

Several studies have suggested a benefit of using antiseptic solutions to irrigate the surgical wound. The most common agent for irrigation is povidone-iodine, which is active against a broad

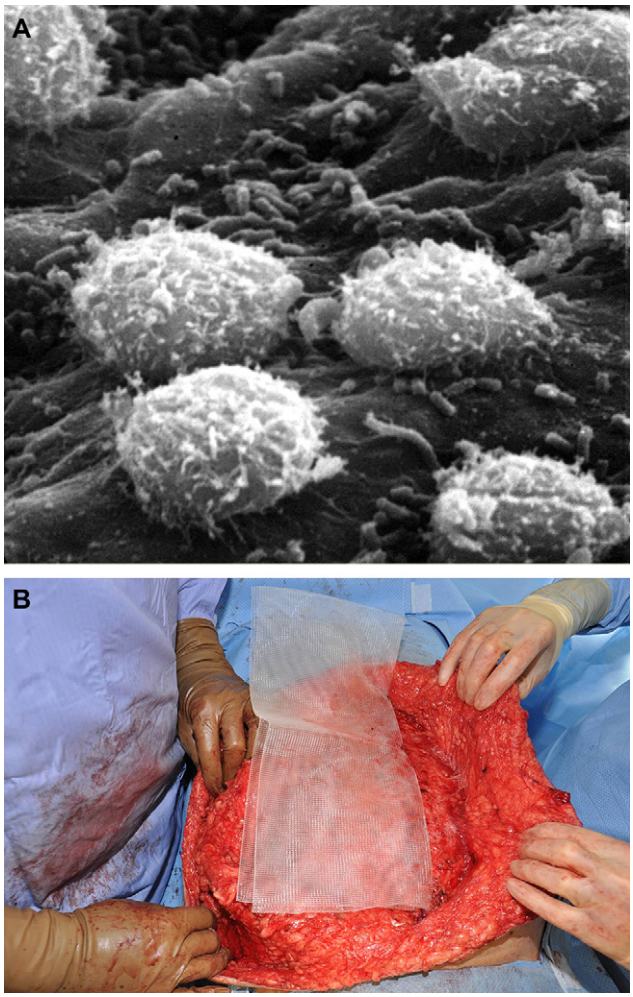


Fig 2. (A) Scanning electron micrograph documenting polymicrobial flora adherent to the serosal mesothelium during fecal peritonitis and host inflammatory response (numerous peritoneal microphage) to contamination (magnification, ×6,000). (B) Implantation of polypropylene mesh for repair of large ventral abdominal defect.

spectrum of wound contaminants. In high concentration (5%) however, povidone-iodine is inhibitory to human fibroblast, having an adverse impact on wound healing.[42,43] A recent retrospective study suggests that a 3-minute dilute (0.35%) povidone-iodine lavage prior to wound closure was an effective strategy for reducing the risk of acute postoperative infection after total joint arthroplasty.[44] A controlled laboratory study found that a 2% chlorhexidine power irrigation was effective at decontaminating tendons without weakening the tendon's tensile mechanical properties.[45] Rare reports of chrondrolysis have been reported following chlorhexidine irrigation, involving high concentrations or prolonged exposure.[46,47] Chlorhexidine at a concentration of 0.05% has been found to be nontoxic to wound healing and granulation tissue.[48] In addition, this concentration has been injected into canine joints with no apparent adverse effect.[49] Whereas a concentration of 0.05% appears to be safe for the surgical wound, is there any evidence to suggest that it would be clinically effective against organisms most often associated with surgical site infections?

In a recent series of in vitro pilot studies (unpublished data), we assessed the antiseptic efficacy of 0.05% CHG: (1) by using time-kill kinetics against selective surgical isolates (Table 1) and (2) by assessing microbial survival on selective biomedical device surfaces

Table 1
Log reduction of selective gram-positive and gram-negative surgical isolates following timed exposure to 0.05% chlorhexidine gluconate solution*

		Log_{10} colony-forming units† (log reduction)	
Organism	CFU‡	60 Seconds	5 Minutes
MRSA	8.7	3.4 (>5 logs)	2.6 (>6 logs)
MSSA	8.4	3.5 (>5 logs)	2.6 (>6 logs)
Staphylococcus epidermidis§	8.3	2.9 (>5 logs)	2.5 (>5 logs)
Escherichia coli	8.8	2.7 (>6 logs)	2.1 (>6 logs)
Escherichia aerogenes	8.9	3.1 (>5 logs)	2.8 (>6 logs)

CFU, Colony-forming units; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-susceptible *Staphylococcus aureus*.
*0.05% Chlorhexidine gluconate (IRRISEPT; IrriMax Corp, Lawrenceville, GA).
†Postexposure: log_{10} CFU/milliliter.
‡Baseline: initial log_{10} CFU/milliliter.
§Biofilm-producing strain from vascular graft infection.

following exposure to 0.05% CHG antiseptic solution (Table 2). Exposure to a concentration of 0.05% CHG effectively produced a 5- to 6-log reduction in microbial recovery at 1 and 5 minutes, respectively (Table 1). This effective log reduction was observed with both gram-positive and gram-negative surgical isolates, including a biofilm-forming strain recovered from a prosthetic device-related infection. Intraoperative irrigation using a safe and effective biocide, especially prior to wound closure, could offer a mechanistic advantage over traditional antibiotic irrigation, which requires a substantially longer period of exposure to the surgical wound. Device implantation has become a common procedure in all surgical services, and, in the case of repair of an abdominal defect with mesh, the open wound can be quite large (Fig 2B), exposing both the tissues and implant to risk of environmental contamination.[50] Table 2 documents the reduction in mean microbial recovery of 3 selective surgical isolates from the surface of 4 separate inert biomedical surfaces. Following a 60-second exposure to 0.05% CHG, there was a significant reduction (P values ranging from $<.05$ to $<.01$) in microbial recovery from the surface of both vascular and abdominal implantable devices. Previous studies have demonstrated that implant devices are highly susceptible to wound contamination, leading to occult infection often presenting weeks or months postoperatively.[51] When a device such as a prosthetic vascular graft is contaminated during insertion, the contaminating flora will down-regulate its metabolism, multiplying slowly on the surface of the device until reaching a critical density at which time the host recognizes that an infectious process is occurring.[51] Irrigating the surgical wound and surface of an implantable device with 0.05% CHG prior to wound closure would likely be an effective and safe risk reduction strategy, a logical alternative to the questionable practice of antibiotic irrigation (lavage). Further clinical studies are warranted to validate the benefit of this potential interventional strategy.

Final consideration: Safety of CHG in the surgical patient population

The incidence of skin hypersensitivity associated with use of CHG has been reported to be rare.[7,52] Preadmission whole-body cleansing and perioperative skin prepping with 2% or 4% CHG has been documented to be a safe and effective risk reduction strategy for preventing surgical site infection.[1,3,4,21-24,26-30] Selected animal models have documented meningeal toxicity following direct application of CHG into neural tissues.[53] In actual clinical practice however, when CHG is allowed to thoroughly dry, it been shown to be a safe, efficacious skin disinfectant and can be used for epidural access and cranial or spinal neurosurgical procedures.[54,55] Vaginal application of CHG in concentrations ranging from 0.05% to 1% has

Table 2
Impact of 0.05% chlorhexidine gluconate on mean microbial recovery of surgical clinical isolates from surface of selective biomedical devices*

Material	MRSA	MSSA	*Staphylococcus epidermidis*† (Baseline/60-sec exposure)‡	*P* value
PTFE§	5.4/1.9	5.6/1.1	6.8/2.2	<.05
Dacron§	6.4/1.2	6.6/1.3	6.5/1.6	<.01
Polyester‖	6.8/2.0	7.1/2.2	7.0/2.1	<.01
Polyester/polylactic acid‖	5.5/1.0	5.9/1.9	6.1/2.4	<.01

MRSA, Methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-susceptible *Staphylococcus aureus*.
NOTE. N = 5 repetitions per device-microbial isolate.
*0.05% chlorhexidine gluconate solution (IRRISEPT; IrriMax Corp, Lawrenceville, GA).
†Biofilm forming strain recovered from vascular graft infection.
‡Mean baseline recovery (log_{10} colony-forming units/cm^2) device surface/postexposure recovery (log_{10} colony-forming units/cm^2) device surface.
§PTFE (polytetrafluoroethylene), Dacron (double-velour) synthetic vascular graft material.
‖Synthetic abdominal mesh material.

been shown to be safe with minimal adverse events.[56,57] Results of a randomized trial comparing 10% povidone-iodine with 4% CHG for vaginal hysterectomy found CHG to be as safe as povidone-iodine for vaginal tissues.[28] However, care should be taken when applying CHG to avoid contact with the middle ear or areas adjacent to the eyes.[58-60] At Froedtert Hospital, patients who shower or cleanse with CHG prior to admission are instructed to avoid getting CHG in the eyes or external ear canal and to immediately rinse if they experience any burning or itching sensation following application.

Is CHG bathing or cleansing an appropriate risk reduction strategy for young children or infants? In adults, CHG is poorly absorbed through intact skin, whereas, in infants and young adults (3 months to 17 years), investigators have detected trace amounts of CHG in blood following skin surface cleansing. However, no evidence was found suggesting that repeat exposure to CHG was associated with systemic accumulation or adverse events.[61,62] The strength of topical CHG concentration does appear to influence detectable levels in the blood: 1% CHG solutions yielded higher blood level than 0.25% or 0.5%.[63] A recent survey of 100 neonatal intensive care units in the United States found that CHG is frequently used (>50%) for central venous catheters, peripherally inserted central catheters (PICC), umbilical line insertions, and central venous catheter maintenance while less frequently used (<10%) for MRSA decolonization or routine bathing.[64] Although it appears that many neonatal intensive care units across the United States are using CHG safely in young infants, CHG is currently not recommended (Food and Drug Administration) for use in infants <2 months of age. The antiseptic benefits of CHG are fully document; however, further studies are warranted assessing the safety and efficacy of CHG preadmission bathing/cleansing in young infants, especially infants less than 2 months of age.

References

1. Holder C, Zellinger M. Daily bathing with chlorhexidine in the ICU to prevent central line associated infections. J Clin Outcome Manage 2009;16:509-13.
2. Rauk PN. Educational intervention, revised instrument sterilization methods, and comprehensive preoperative skin preparation protocol reduce cesarean section surgical site infections. Am J Infect Control 2010;38:319-23.
3. Sviggum HP, Jacob AK, Arendt KW, Mauermann ML, Horlocker TT, Hebl JR. Neurologic complications after chlorhexidine antisepsis for spinal anesthesia. Reg Anesth Pain Med 2012;37:139-44.
4. Hibbard JS. Analysis comparing the antimicrobial activity and safety of current antiseptic agents: a review. J Infus Nurs 2005;28:194-207.
5. Johnson AJ, Kapadia BH, Daley JA, Moline CB, Mont MA. Chlorhexidine reduces infections in knee arthroplasty. J Knee Surg. 2012 Nov 12 [Epub ahead of print].
6. Milstone AM, Passaretti CL, Perl TM. Chlorhexidine expanding the armamentarium for infection control and prevention. Clin Infect Dis 2008;46:274-81.
7. Edmiston CE, Seabrook GR, Johnson CP, Paulson DS, Beausoleil C. Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as a topical antiseptic for preparation of the skin prior to surgery. Am J Infect Control 2007;35:89-96.
8. Edmiston CE, Okoli O, Graham MB, Sinski S, Seabrook GR. Evidence for using chlorhexidine gluconate preoperative cleansing to reduce the risk of surgical site infections. AORN J 2010;92:509-18.
9. Harbison MA, Hammer SM. Inactivation of human immunodeficiency virus by betadine products and chlorhexidine. J Acquir Immune Defic Syndr 1989;2:16-9.
10. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action and resistance. Clin Microbiol Rev 1999;12:147-79.
11. Hugo WB, Longworth AR. Some aspects of the mode of action of chlorhexidine. J Pharm Pharmacol 1964;16:655-62.
12. Barry AL, Fuch PC, Brown SD. Lack of effect of antimicrobial resistance on susceptibility of microorganisms to chlorhexidine gluconate or povidone iodine. Diagn Microbiol Infect Dis 1999;18:920-1.
13. Wang JT, Sheng WH, Wand JL, Chen D, Chen ML, Chen YC, et al. Longitudinal analysis of chlorhexidine susceptibility of noscomial methicillin-resistant *Staphylococcus aureus* isolates at a teaching hospital in Taiwan. J Antimicrob Chemother 2008;62:514-7.
14. Zhang M, O'Donoghue MM, Ito T, Hiramatsu K, Boost MV. Prevalence of antiseptic-resistance genes in *Staphylococcus aureus* and coagulase-negative staphylococci colonizing nurses and the general population in Hong Kong. J Hosp Infect 2011;78:113-7.
15. 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.
16. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. The Hospital Infection Control Practice Advisory Committee: guidelines for the prevention of surgical site infections. Am J Infect Control 1999;27:97-132.
17. Paulson DS. Efficacy evaluation of a 4% chlorhexidine gluconate as a full-body shower or wash. Am J Infect Control 1993;21:205-9.
18. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection (review). Cochrane Database Syst Rev; 2007:CDO004985.
19. Chlebicki MJP, Safdar N, O'Horo JC, Maki DG. Preoperative chlorhexidine shower or bath for prevention of surgical site infection. Am J Infect Control 2013;41:167-73.
20. Jakobsson J, Perlkvist A, Wann-Hansson C. Searching for evidence regarding using preoperative disinfection showers to prevent surgical site infections: a systematic review. Worldviews on Evidence-Base Nurs 2011;(3rd quarter):143-52.
21. Edmiston CE, Krepel CJ, Seabrook GR, Lewis BD, Brown KR, Towne JB. Preoperative shower revisited: can high topical antiseptic levels be achieved on the skin surface before surgical admission. J Am Coll Surg 2008;207:233-9.
22. Eiselt D. Presurgical skin preparation with a novel 2% chlorhexidine gluconate cloth reduces rates of surgical site infection in orthopedic surgical patients. Orthop Nurs 2009;28:141-5.
23. Lipke VL, Hyott AS. Reducing surgical site infections by bundling mulriple risk reduction strategies and active surveillance. AORN J 2010;92:288-96.
24. Kim DH, Spencer M, Davidson SM, Li L, Shaw JD, Gulczynski D, et al. Institutional prescreening for detection and eradication of methicillin-resistant *Staphylococcus aureus* in patients undergoing elective orthopedic surgery. J Bone Joint Surg 2010;92:1820-6.
25. Ramos N, Skeets F, Haas JP, Hutzler L, Slover J, Phillips N, et al. Surgical site infection prevention initiative: patient attitude and compliance. Bull NYU Hosp Joint Dis 2011;69:312-5.
26. Ostrander RV, Botte MJ, Brage ME. Efficacy of surgical preparation solution in foot and ankle surgery. J Bone Joint Surg 2005;87:980-5.
27. Saltzman MD, Nuber GW, Gryzlo SM, Marecek GS, Kol JL. Efficacy of surgical preparations in shoulder surgery. J Bone Joint Surg 2009;91:1949-53.
28. Culligan PJ, Kubik K, Murphy M, Blackwell L, Snyder J. A randomized trial that compared povidone iodine and chlorhexifine as antiseptics for vaginal hysterectomy. Obstet Gynecol 2005;192:422-5.
29. Savage JW, Weatherford BM, Sugrue PA, Nolden MT, Liu JC, Song JK, et al. Efficacy of surgical preparation solution in lumbar surgery. J Bone Joint Surg 2012;94:490-4.
30. Swenson BR, Hedrick TL, Metzger R, Bonatti H, Pruett TL, Sawyer RG. Effect of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin prepping protocols. Infect Control Hosp Epidemiol 2009;30:964-71.
31. Darouiche RO, Wall MJ, Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. N Eng J Med 2010;362:18-26.
32. Lee I, Agarwal RK, Lee BY, Fishman NO, Umscheid CA. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. Infect Control Hosp Epidemiol 2010;31:1219-29.
33. Edmiston CE, Goheen MP, Kornhall S, Jones FE, Condon RE. Fecal peritoinitis: microbial adherence to serosal mesothelium and resistance to peritoneal lavage. World J Surg 1990;14:176-83.
34. Crowley DJ, Kanakaris NK, Giammoudis PV. Irrigation of the wounds in open fractures. J Bone Joint Surg 2007;89B:580-5.

35. Price J. Surgical intervention in cases of generalized peritonitis. Proc Phila County Med Soc 1905;26:192-5.
36. Torek F. The diagnosis and treatment of pertitonitis of the upper abdomen. Boston Med J Surg 1910;162:484-9.
37. Damm S. Intraoperative anaphylaxis associated with bactracin irrigation. Am J Health-Syst Pharm 2011;68:323-7.
38. Michels M, Aggers WA. Prophylactic use of topical antibiotic irrigation for clean surgical wounds. Gundersen Lutheran Med J 2003;2:31-3.
39. Moore CB, Smith RS, Herbertson R, Toevs C. Does use of intraoperative irrigation with open or laparoscopic appendectomy reduce post-operative intra-abdominal abscess. Am Surg 2011;77:78-80.
40. Parcells JP, Mileski JP, Gnagy FT, Haragan AF, Mileski WJ. Using antimicrobial solution for irrigation in appendicitis to lower surgical site infection rates. Am J Surg 2009;198:875-80.
41. Koyonos L, Zmistowski B, Della- Valle CJ, Parvizi J. Infection control rate of irrigation and debridement of periprosthetic joint infection. Clin Orthop Relat Res 2011;469:3043-8.
42. Vilijanto J. Disinfection of surgical wounds without inhibition of normal wound healing. Arch Surg 1980;115:253-6.
43. Lineaweaver W, McMorris S, Soucy D, Howard R. Cellular and bacterial tocixity of topical antimicrobials. Plast Reconstr Surg 1985;75:394-6.
44. Brown NM, Cipriano CA, Moric M, Sporer SM, Della-Valle CJ. Dilute betadine lavage before closure for the prevention of acute postoperative deep periprosthetic joint infection. J Arthroplasty 2012;27:27-30.
45. Han Y, Giannitsios D, Duke K, Steffen T, Burman M. Biomechanical analysis of chlorhexidine power irrigation to disinfect contaminated anterior cruciate ligament grafts. Am J Sports Med 2012;39:1528-33.
46. Douw CM, Bulstra SK, Vandenbroucki J, Geesink RG, Vermeulem A. Clinical and pathological changes in the knee after accidental chlorhexidine irrigation during arthroscopy: case report and review of literature. J Bone Joint Surg 1998;80:437-40.
47. Van Huyssteen AL, Bracey DJ. Chlorhexidine and chrondrolysis in the knee. J Bone Joint Surg 1999;81:995-6.
48. Best AJ, Nixon MF, Taylor GJ. Brief exposure of 0.05% chlorhexidine does not impact non-osteoarthritic human cartilage metabolism. J Hosp Infect 2007;67: 67-71.
49. Anderson MA, Payne JT, Kreeger JM, Wagner-Mann CC, Schmidt DA, Mann FA. Effect of intra-articular chlorhexidine diacetate lavage on the stifle in healthy dogs. Am J Vet Res 1993;54:1784-9.
50. Munoz-Price LS, Birnbach DJ, Lubarsky DA, Arheart KL, Fajardo-Aquino Y, et al. Decreasing operating room environmental pathogen contamination through improved cleaning practices. Infect Control Hosp Epidemiol 2012;33:897-904.
51. Edmiston CE. Prosthetic device infections in surgery. In: Nichols RL, Nyhus LM, editors. Update surgical sepsis. Philadelphia [PA]: J.B. Lippincott Co; 1993.
52. Rosenberg A, Alatary SD, Peterson AF. Safety and efficacy of antiseptic chlorhexidine gluconate. Surg Gynecol Obstet 1978;143:789-92.
53. Henschen A, Olson L. Chlorhexidine-induced degeneration of adrenergic nerves. Acta Neuropathol 1984;63:18-23.
54. Kinirons B, Mimoz O, Lafendi L, Naas T, Meunier J, Nordmann P. Chlorhexidine versus povidone iodine in preventing colonization of continuous epidural catheters in children: a randomized, controlled trial. Anesthesiology 2001;94: 239-44.
55. Grewel S, Hocking G, Wildsmith JA. Epidural abscesses. Br J Anesthesiol 2006; 96:292-302.
56. Goldenberg RL, McClure EM, Saleem S, Rouse D, Vermund S. Use of vaginally administered chlorhexidine during labor to improve pregnancy. Obstet Gynecol 2006;107:1139-46.
57. Rouse DJ, Hauth JC, Andrews W, Mills BB, Maher JE. Chlorhexidine vaginal irrigation for the prevention of peripartal infection: a placebo-controlled, randomized clinical trial. Am J Obstet Gynecol 1997;176:617-22.
58. Keser A, Bozkurt M, Taner OF, Yorgancigil B, Dogan M, Sensoz O. Evaluation of antiseptic use in plastic and hand surgery. Ann Plast Surg 2005;55:490-4.
59. Hamed LM, Ellis FD, Boudreault G, Wilson FM, Halveston EM. Hibiclens keratitis. Am J Ophthalmol 1987;104:50-6.
60. Phinney RB, Modino BJ, Hofbauer JD, Meisler DM, Langston LH, Benes SC. Corneal edema related to accidental Hibiclens exposure. Am J Ophthalmol 1988;106:210-5.
61. Case DE. Chlorhexidine: attempts to detect percutaneous absorption in man. Proc Int Congress Chemother 1976;3:367-74.
62. Lee A, Harlan R, Breaud AR, Speck K, Perl TM, Clarke W, et al. Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infect Control Hosp Epidemiol 2011;32:395-7.
63. Mullany LC, Khatry SK, Sherchand JB, Leclerq SC, Darmstadt GL, Katz J, et al. A randomized, controlled trial of the impact of chlorhexidine skin cleansing on bacterial colonization of hospital-born infants in Nepal. Pediatr Infect Dis J 2008;27:505-11.
64. Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. J Perinatol 2012;32:4-9.