


Review

Use of Chlorhexidine Preparations in Total Joint Arthroplasty

Jaiben George, Alison K Klika, Carlos A Higuera 

Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, OH, USA

 Corresponding author: Dr. Carlos A Higuera, MD, higuerc@ccf.org.

© Ivyspring International Publisher. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY-NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>). See <http://ivyspring.com/terms> for full terms and conditions.

Published: 2017.01.01

Abstract

Prosthetic joint infection (PJI) is a serious complication after total joint arthroplasty (TJA). Chlorhexidine is a widely used antiseptic because of its rapid and persistent action. It is well tolerated and available in different formulations at various concentrations. Chlorhexidine can be used for pre-operative skin cleansing, surgical site preparation, hand antisepsis of the surgical team and intra-articular irrigation of infected joints. The optimal intra-articular concentration of chlorhexidine gluconate in irrigation solution is 2%, to provide a persistent decrease in biofilm formation, though cytotoxicity might be an issue. Although chlorhexidine is relatively cheap, routine use of chlorhexidine without evidence of clear benefits can lead to unnecessary costs, adverse effects and even emergence of resistance. This review focuses on the current applications of various chlorhexidine formulations in TJA. As the treatment of PJI is challenging and expensive, effective preparations of chlorhexidine could help in the prevention and control of PJI.

Key words: Prosthetic joint infection, total joint arthroplasty

Background

With surgical advancements in total joint arthroplasty (TJA), the incidence of complications after TJA has considerably decreased. However, prosthetic joint infection (PJI) remains a serious complication after TJA and an increasing proportion of revisions are being performed for PJI [1]. Advances in infection control practices like laminar flow operating rooms, methicillin resistant *Staphylococcus aureus* (MRSA) screening, preoperative skin cleansing and antimicrobial prophylaxis have been shown to be effective [2]. Despite these measures, infection remains as a major cause of morbidity and mortality among TJA patients. This may be partially explained by the emergence of antibiotic resistant organisms and the increasing number of TJA patients who are elderly and have a high number of comorbidities, which increases the risk of wound complications and infection [3,4]. PJI occurring in the first three months after TJA are usually caused by virulent

microorganisms such as *Staphylococcus aureus*, whereas delayed infections (3-24 months after surgery) are usually caused by low virulent microorganisms such as coagulase-negative *Staphylococci* [5]. Skin is recognized as the major source of both these organisms. Pathogenic organisms residing on the skin can reach implants during the time of surgery or through the blood from a distant source [6]. Since the early work of Joseph Lester, the importance of skin antisepsis to prevent surgical site infections (SSI) have been recognized in the medical field [7]. A number of antiseptic formulations are currently available to decrease the skin microbial load during the time of surgery. Chlorhexidine is a widely used skin and mucus membrane antiseptic and is active against a broad spectrum of organisms. This review focuses on the current applications of various chlorhexidine formulations in TJA and the evidence in support of the use of chlorhexidine.

Table 1. Common applications of chlorhexidine gluconate (CHG) in total joint arthroplasty.

Use	Commercially available CHG preparations	Current evidence	International Consensus on Periprosthetic Joint Infection [49]
Preoperative skin cleansing	Shower: 4% CHG solution (Hibiscrub®, BactoShield®) Cloth: 2% CHG (SAGE® products)	Evidence based on mostly observational studies. Clear reduction in skin bacterial load. Reduction in surgical site infection is less convincing. Multiple applications are required. Better compliance could be seen with cloths compared to showers.	Whole body cleansing with CHG starting at least the night before surgery (Strong Consensus)
Surgical site preparation	2% CHG and 70% isopropyl alcohol (Chloraprep®)	Some evidence suggesting superiority of CHG with alcohol over other preparations.	No single agent recommended. Combination with alcohol preferred. (Strong Consensus)
Hand antisepsis	4% CHG scrub (BD E-Z Scrub™), 1% CHG and 61% ethyl alcohol (Avagard™)	No clear difference between CHG based scrubs and other antiseptics.	Mechanical hand wash for at least 2 minutes. No agent recommended. (Strong Consensus)
Irrigation solution	0.05% CHG solution (Irrisept®)	Have bactericidal and anti-biofilm properties. But, can be cytotoxic at even low concentrations. Clinical utility yet to be established.	Not Available

Mechanism of Action

Chlorhexidine is a bisbiguanide and exists as a cationic form at physiological pH that binds to the negatively charged bacterial cell wall, altering the osmotic equilibrium of the bacterial cell [8,9]. Chlorhexidine is water insoluble and the commercially available chlorhexidine is usually formulated with gluconic acid to form water soluble salts for clinical applications [8]. Chlorhexidine gluconate (CHG) is available in a variety of concentrations (0.5%–4%) and formulations (wipes, cloths, scrubs, solutions) (Table 1). It is available as either a single agent or in combination with alcohol (isopropyl alcohol or ethyl alcohol) [9]. It is bacteriostatic at low concentrations (0.0002% to 0.5%) and is bactericidal at much higher concentrations (>0.5%) [9,10]. At lower concentrations, it disrupts cellular membranes resulting in leakage of cell contents. At higher concentrations, chlorhexidine can cause coagulation of intracellular contents. Although very high concentrations of chlorhexidine can result in ATPase inactivation, the lethal effects of chlorhexidine are primarily mediated by membrane disruptive properties [11]. It has broad spectrum activity and is highly effective against a wide variety of organisms responsible for PJI, like *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and coagulase negative *Staphylococcus*. It also demonstrates activity against gram-negative bacteria, fungi and to a lesser extent, mycobacteria. It is sporostatic, but not sporicidal [9]. Chlorhexidine is up taken by the bacteria at an extremely rapid rate with the maximum uptake occurring within 20 seconds [12]. The uptake is possibly due to passive diffusion and is concentration dependent [13]. Very little additional binding occurs with increased exposure times and most of the bactericidal effects of CHG occurs immediately

following contact with the bacteria [14]. However, CHG retains its antimicrobial activity for long durations and can thus prevent further bacterial surface attachment and growth. The antimicrobial activity of CHG has been documented to persist up to 48 hours of contact with skin [15]. This rapid and persistent action of chlorhexidine makes it an ideal antiseptic for pre-operative skin preparation.

Preoperative Skin Cleansing

Skin colonization provides a reservoir from which bacteria can be introduced when the skin barrier is breached by shaving, aspiration, or surgery. Colonization clearly increases the risk for subsequent infection [16]. Skin preparation during surgery is limited to the operative field. However, skin flora of the remaining skin can also act as source of infection [6]. A preoperative antiseptic shower or bath can decrease skin microbial load significantly and has been suggested to decrease the incidence of SSIs. In a prospective study of more than 700 patients, Garibaldi [17] showed that patients who received preoperative antiseptic showers with CHG compared to povidone-iodine or regular soap had a significantly higher reduction in skin bacterial load. Although other studies support the role of CHG showers in reducing bacterial count, the role of CHG in decreasing wound infection rates is controversial [18,19]. Hayek et al [20] demonstrated that CHG showers decreased the risk of infection compared to conventional bar soap or placebo. However, the clinical efficacy of CHG showers have been questioned in a number of other studies [21,22]. In a Cochrane review, preoperative showering or bathing with CHG failed to show any benefit over other wash products in reducing SSIs [23]. The contrasting findings across studies could be due to the variability in the protocols for bathing in the different studies. For example, multiple applications of CHG can be

superior to a single application as the antibacterial effect of chlorhexidine is cumulative [19]. Chlorhexidine can adhere to skin and remain on the skin even after rinsing and drying. With repeated applications, chlorhexidine accumulates on skin to produce higher concentrations resulting in increased immediate bacterial reductions, a property termed cumulative effect [24,25]. Paulson et al [18] evaluated the effect of daily CHG showers over 5 days and found that greater reductions in microbial counts were observed as the study progressed. Furthermore, contrasting findings across studies can be a result of the heterogeneity in the study populations with respect to risk factors for wound infection. Nasal carriage of *S. aureus* is known to be a risk factor for bacteremia and subsequent development of infection [6]. Numerous studies have demonstrated *S. aureus* decolonization protocols can decrease the incidence of infections after TJA [26,27]. In a multicenter, double-blinded, randomized controlled trial (RCT), Bode et al showed that patients with *S. aureus* nasal carriage who were treated prophylactically with mupirocin nasal ointment and CHG soap had a significantly lower risk of SSIs [28]. Since most of the decolonization protocols involved the use of CHG as an adjunctive to other measures, it is difficult to establish the independent effects of CHG showers. But, it is likely that the effects of preoperative CHG shower might be pronounced in patients with certain risk factors for infection like *S. aureus* colonization. Kapadia et al stratified total knee arthroplasty (TKA) patients based on the risk of wound infection and demonstrated that the benefits of preoperative CHG was predominantly observed in medium and high risk patient populations [29].

Since preoperative CHG bathing is patient dependent, the reproducibility of this practice is concerning. Despite the efforts to educate patients regarding preoperative bath, it is difficult to ensure compliance to the regimens [30,31]. Cloths have been recently advocated as these are relatively simpler to use, resulting in better patient compliance. CHG impregnated cloths are commercially available and patients are given instructions to use these clothes before TJA. In a study by Edmiston et al [32] which compared the bacterial concentration at various skin sites after CHG shower and CHG cloth, it was found that cloth resulted in higher concentrations of CHG at the skin. They also showed that certain skin sites attained sub therapeutic concentrations of CHG with use of shower, while cloths were able to achieve higher concentrations uniformly across multiple skin sites. The reasons for the superior efficacy of cloths are unclear and probably due to better compliance and the design of the cloth allowing for better skin

penetration [33]. In an observational study by Eiselt [34], incidence of SSI following TJA after the introduction of 2% CHG cloth reduced by 50%. In a prospective study evaluating infection rates after total hip arthroplasty (THA), patients who were compliant to the CHG cloth regimen had lower rates of SSI [33]. Similar results were obtained in TKA patients [35]. In two studies of more than 3,000 patients each, Kapadia et al [29,36] showed that preoperative CHG cloths administered on the evening before surgery and morning resulted in statistically significant reduction in SSI after both TKA and THA. However, none of the studies were performed in a randomized controlled manner. On the contrary, Farber et al [37] found that introduction of CHG impregnated wipes in the pre-surgical setting was not associated with a reduced SSI incidence. The contrasting findings could be due to the differences in the protocol for CHG application. In the study by Farber et al [37], a nurse applied the CHG wipes which ensured 100% compliance in the patients. However, the application was only limited to the morning of surgery in the pre-surgical setting, while in the studies by Kapadia et al [29,36] CHG was applied the night before and on the morning of surgery. Since chlorhexidine is shown to exert a cumulative effect with repeated applications, it is possible that multiple applications might be necessary to significantly reduce surgical site infections. Additionally, in the study by Farber et al [37], preoperative cleansing was limited to the surgical area only. In a large RCT, whole body CHG cleansing was shown to be superior in decreasing SSI rates compared to local cleansing alone, suggesting that preoperative skin cleansing with CHG should include the whole body to provide desired benefits [38].

Surgical Site Preparation

Transient pathogenic skin flora present at the time of incision can be easily removed by a number of antiseptic agents. The iodophors (e.g., povidone-iodine), alcohol-containing products and chlorhexidine are the most commonly used agents for surgical skin preparation [7]. Although CHG is the preferred agent to prevent catheter related infection, the preferred antiseptic agent for surgical site preparation is less obvious [7]. Alcohol is readily available, inexpensive, and has the fastest onset of action, while chlorhexidine has the greatest residual antimicrobial activity [39]. One major disadvantage of the use of alcohol in the operating room is its inflammability [39]. CHG is not inactivated by blood while iodophors may be inactivated by blood or serum proteins [39,40]. A number of studies have shown the superiority of CHG preparations in decreasing the bacterial load compared to iodine

based products [41–44]. However, it is unclear whether this superiority of CHG in decreasing the microbial load is clinically relevant as the observed reduction in bacterial load do not necessarily result in a reduction of SSI [43,45]. In a single institution prospective series of all surgical patients, Swenson et al [46] assessed the SSI rates after sequential implementation of skin preparation with one of the three protocols: povidone-iodine with isopropyl alcohol, CHG in isopropyl alcohol and iodine povacrylex in isopropyl alcohol. The authors found a significantly higher post-operative infection rate during the period when CHG was used. On the contrary, in a large multicenter RCT, Darouiche et al [47] showed that using 2% CHG with 70% isopropyl alcohol resulted in significantly lower rates of SSI compared to 10% povidone-iodine paint, though alcohol was not used in povidone-iodine. In a large comprehensive meta-analysis of RCTs, it was found that CHG-alcohol was superior to alcohol-based povidone iodine paint [48]. However, this was based on a single inadequately reported study and the included trials significantly differed in the skin preparation protocols, limiting the ability to make definite conclusions. Additionally, no studies have adequately assessed the comparative effects of various preoperative skin antiseptics on SSI risk following TJA. Due to the lack of conclusive evidence to support one or the other antiseptic, the International Consensus on PJI (ICPJI) recommends using alcohol based antiseptic containing either CHG or iodine [49]. The updated guidelines from Centers for Disease Control and Prevention (CDC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) also recommend the use of alcohol based products for surgical site preparation unless contraindicated [50].

Hand Antisepsis

Surgeons and assistants routinely carry out hand asepsis before surgery to decrease transfer of bacteria to patients' wound. The two most common forms of hand antisepsis involve hand scrubbing and hand rubbing [51]. Scrubbing is conducted using aqueous solutions containing antiseptic ingredients such as CHG or povidone iodine, while rubbing involves alcohol based products which are left to evaporate. The most effective protocol and the desired agent for surgical hand antisepsis are still unclear. Alcohol is effective against a wide range of bacteria and other micro-organisms and cause an immediate reduction of 95% of the resident flora and a 99% reduction with repeated applications [13]. Chlorhexidine can be left on the hands, and it will continue to lower bacterial counts during the procedure [52]. CDC recommends

2-5 minutes of surgical scrub of hands and forearms up to the elbow, though the antiseptic of choice is not mentioned [7]. In a multicenter RCT, Parienti et al [53] demonstrated that hand-rubbing with aqueous alcoholic solution, preceded by a 1-minute non-antiseptic hand wash was as effective as traditional hand-scrubbing with antiseptic soap (4% povidone iodine or 4% CHG) in preventing surgical site infections. However, no direct comparisons were performed between CHG and povidone iodine, and alcohol. In a meta-analysis of 14 clinical trials, Tanner et al [54] showed that CHG scrubs may reduce the number of bacterial colony forming units (CFUs) on hands compared with povidone iodine scrubs; however, it failed to show significant reduction in the rates of SSI. Also, they concluded that alcohol rubs with additional antiseptic ingredients like CHG may reduce bacterial CFUs compared with aqueous scrubs [54]. The ICPJI states that there are no clear differences between various protocols and agents and hence do not recommend any particular agent, although it recommends hand washing for at least 2 minutes [49].

Irrigation Solution

Extensive debridement with or without antiseptic irrigation is an important step in the revision of infected joints. While irrigation is one among the many steps in revisions with component removal, it is probably the most important step in revisions with component retention. Despite the large amount of literature dealing with the outcomes of irrigation and debridement, little is known about the best irrigation solution to use. There is no clear consensus on the protocol or the irrigation solution to be used for debridement of infected joints [55]. Normal saline (NS), castile soap, bacitracin solution, CHG, betadine and hypochlorite are some commonly used irrigation solutions [56,57]. Most surgeons use a combination of irrigation solutions for the management of PJI [58]. However, there is little evidence to support the use of any antiseptic or antibiotic solution compared to NS alone [59,60]. In a large multicenter RCT comparing irrigation protocols of open fractures, irrigation with NS resulted in lower rates of infection than castile soap solution and low pressure was equally effective as the high pressure NS irrigation [59]. In another RCT, bacitracin solutions offered no advantage over NS irrigation in decreasing wound infection after open fractures, though wound healing problems were higher in bacitracin treated patients [60]. Schwechter et al [61] showed that CHG solutions could be potentially used to decrease biofilm load on orthopedic implants using an *in vitro* model of MRSA infection. In a later study published by the same group, the optimal concentration of CHG

was evaluated and it was demonstrated that concentrations above 2% was required to provide persistent decrease in the biofilm [62]. Although lower concentrations of CHG decreased biofilm, there was a rebound growth of biofilm with prolonged incubation suggesting that the lower concentrations are likely to be ineffective in vivo. However, concentrations of CHG as low as 0.02% can be cytotoxic to human fibroblasts [63]. In an *in vitro* study, dilute povidone-iodine was found to be the optimal irrigation agent due to its low toxicity at bactericidal concentrations [63]. While other antiseptics, like CHG and hydrogen peroxide, were found to be bactericidal at commercially available concentrations, cytotoxic effects on human fibroblasts and mesenchymal stromal cells were noted at their minimum bactericidal concentrations (MBC). Despite the lack of sufficient evidence in favor of one or the other irrigation solutions, many antiseptics are routinely used for irrigation of the infected joint due to perceived benefits of antiseptic solutions. In a survey of 186 orthopedic surgeons, the majority of the surgeons responded that they regularly use antibiotics in irrigation solutions [64]. The current orthopedic literature is lacking enough information regarding the appropriate volume, technique, and type of irrigation fluid, and much of the practice is based on experience rather than evidence.

Novel Applications

Maintaining a clean wound post-operatively is equally as important as preoperative and intraoperative measures to reduce bacterial load at the operative site. Although, there is a theoretical risk of the wound acting as portal of entry for skin microbes, there is insufficient data to support the routine prophylactic use of antimicrobial coated dressings [65,66]. CHG impregnated dressings have not been studied in detail, and most of the literature on antimicrobial dressings in TJA deals with silver impregnated dressings. CHG coated adhesives can result in significant reduction of the skin resident flora compared to non-antimicrobial adhesives, especially when the dressings are used for prolonged periods [67]. In a meta-analysis of nine trials, CHG-impregnated dressings were found to be beneficial in preventing catheter colonization and, more importantly, catheter-related bloodstream infection [68]. In a retrospective study of patients undergoing foot and ankle surgery with external fixators, CHG dressings were shown to decrease the rates of pin infections [69]. CHG coated sutures have also been developed [70]. It is proposed that these could be useful in cases of triclosan resistance. Triclosan is a broad spectrum antiseptic, and triclosan

coated sutures have been shown to decrease SSI, especially in abdominal surgeries [71]. However, the potential benefits of these experimental applications of CHG are doubtful and have yet to be studied in TJA population.

Resistance

A number of studies have recently reported that the prevalence of bacteria with reduced susceptibilities to chlorhexidine is increasing [72–76]. Resistance is mediated through reduced permeability of chlorhexidine, inactivation of the chlorhexidine molecule and efflux mechanisms [75]. Additionally, the presence of organic matter, altered pH and biofilm can result in reduced susceptibilities to chlorhexidine [9]. Since sub-therapeutic concentrations may be linked to emergence of resistance, the residual activity of chlorhexidine could promote resistance in resident skin flora. The prevalence of the genes mediating resistance in coagulase negative *Staphylococci* species was found to be higher in isolates from nurses compared with those from the general population, indicating that the hospital environment could exert selective pressure for emergence of resistant strains [76]. Multi drug resistant strains of organisms commonly encountered in PJI like MRSA have been shown to exhibit reduced susceptibility to chlorhexidine [72–74]. This is of particular concern given the widespread use of chlorhexidine for the purposes of MRSA decolonization before TJA [26]. Although MRSA may be associated with higher chlorhexidine minimum inhibitory concentration (MIC) or MBC than MSSA, the clinical relevance of this finding is not fully established [77]. The concentrations achieved when chlorhexidine is used as recommended by the manufacture are several orders of magnitude higher than the MBC of *S. aureus* [78]. Cookson et al showed that chlorhexidine remains effective at killing *S. aureus* that have an elevated chlorhexidine MIC, questioning the clinical importance of elevated MIC [77]. Although chlorhexidine has been widely used in clinical practice for more than five decades, resistance does not appear to be a major problem. However, every effort should be made to prevent unnecessary and improper use of chlorhexidine to prevent such issue.

Adverse Effects

CHG has been extensively used as a skin and mucous membrane disinfectant due to its excellent tolerability. CHG is poorly absorbed through intact adult skin [79]. Since most uses of chlorhexidine are limited to intact skin, very few adverse events have been reported for CHG [9]. The most frequent adverse reaction to chlorhexidine is contact dermatitis [9].

However, serious adverse reactions like anaphylaxis are being increasingly reported with the use of CHG [9,80]. As CHG is a common antiseptic agent used in medical practice and personal hygiene products, there is a potential for sensitization to CHG in the general population which can result in serious hypersensitivity reactions [80]. Most of the serious reactions to CHG have been associated with the use of CHG on mucous membranes [80,81]. For example, a severe anaphylactic reaction was reported in a patient sensitized to CHG present in the gel used to insert a urinary catheter, requiring the patient's hip replacement surgery to be postponed [82]. CHG solution has also been shown to be cytotoxic to human fibroblast, osteoblasts and lymphocytes in a time and dose dependent manner [83–85]. The potential adverse local and systemic effects from intra-articular use of CHG remain largely uninvestigated. Accidental irrigation of 1% CHG during knee arthroscopy was reported to result in extensive chondrolysis in a case series of five patients [86]. In an *in vitro* study, very low concentrations of chlorhexidine that have little effect on cellular proliferation was shown to significantly reduce both collagen and non-collagen protein production of human gingival fibroblasts [83]. Therefore, intra articular irrigation with even dilute concentrations of chlorhexidine for short periods of time can have serious toxic effects on collagen producing cells and might result in delayed wound healing.

Cost Effectiveness

The treatment of PJI is extremely challenging and imposes a heavy burden on the healthcare system. The annual cost of infected revisions to US hospitals had increased in the recent years and is projected to exceed \$1.6 billion by 2020 [87]. Utilizing antiseptics, including CHG, are considered as key steps in surgical procedures including TJA are relatively cheap. However, with increasing focus being placed on cost effective interventions, it is important to choose the most effective antiseptic protocol. In a systematic review, Lee et al concluded that chlorhexidine is more effective in surgical site antisepsis than iodine and results in significant cost savings [88]. Pre-operative use of chlorhexidine cloths has recently gained popularity and is routinely employed to decrease the skin microbial load. Since PJI is an expensive condition and use of CHG cloths is relatively cheap, CHG cloths could be a cost-effective intervention even if marginally effective. In one study, CHG cloths were demonstrated to decrease healthcare costs, resulting in a net savings of approximately \$2 million per 1,000 TKA [89].

Conclusions

PJI is a serious complication after TJA with significant morbidity and mortality. Simple, cheap and effective strategies to prevent PJI can improve the outcomes of TJA and result in significant cost savings. CHG is available in a number of different formulations and concentrations, and it has been used in medical practice for a very long time. Despite its proven antiseptic effects, the current literature is limited by the lack of high quality trials which can provide definitive answers regarding the clinical effectiveness of various CHG preparations in preventing and treating PJI. However, given the relative safety of CHG products and limited emergence of resistance, pre-operative skin preparation with CHG appears to be a beneficial intervention in decreasing the incidence of PJI. CHG preparations containing alcohol is an effective antiseptic for surgical site preparation as well as hand antisepsis, although the superiority over povidone-iodine is not fully conclusive. Antimicrobial solutions are increasingly being used for intra-articular irrigation, and further research is necessary to establish the safety and effectiveness of CHG containing irrigation solutions.

Competing Interests

The authors have declared that no competing interest exists.

References

- [1] Jämsen E, Furnes O, Engesaeter LB, Konttinen YT, Odgaard A, Stefánsdóttir A, et al. Prevention of deep infection in joint replacement surgery. *Acta Orthop* 2010;81:660–6. doi:10.3109/17453674.2010.537805.
- [2] Kapadia BH, Berg RA, Daley JA, Fritz J, Bhavre A, Mont MA. Periprosthetic joint infection. *Lancet* (London, England) 2016;387:386–94. doi:10.1016/S0140-6736(14)61798-0.
- [3] Odum SM, Springer BD, Dennos AC, Fehring TK. National obesity trends in total knee arthroplasty. *J Arthroplasty* 2013;28:148–51. doi:10.1016/j.arth.2013.02.036.
- [4] Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. *J Arthroplasty* 2008;23:984–91. doi:10.1016/j.arth.2007.10.017.
- [5] Trampuz A, Widmer AF. Infections associated with orthopedic implants. *Curr Opin Infect Dis* 2006;19:349–56. doi:10.1097/01.qco.0000235161.85925.e8.
- [6] von Eiff 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. doi:10.1056/NEJM200101043440102.
- [7] Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999;27:97–132; quiz 133–4; discussion 96.
- [8] Lim K-S, Kam PCA. Chlorhexidine—pharmacology and clinical applications. *Anaesth Intensive Care* 2008;36:502–12.
- [9] Milstone AM, Passaretti CL, Perl TM. Chlorhexidine: expanding the armamentarium for infection control and prevention. *Clin Infect Dis* 2008;46:274–81. doi:10.1086/524736.
- [10] Oosterwaal PJ, Mikx FH, van den Brink ME, Renggli HH. Bactericidal concentrations of chlorhexidine-digluconate, amine fluoride gel and stannous fluoride gel for subgingival bacteria tested in serum at short contact times. *J Periodontol Res* 1989;24:155–60.
- [11] Barrett-Bee K, Newbould L, Edwards S. The membrane destabilising action of the antibacterial agent chlorhexidine. *FEMS Microbiol Lett* 1994;119:249–53.
- [12] Fitzgerald KA, Davies A, Russell AD. Uptake of 14C-chlorhexidine diacetate to *Escherichia coli* and *Pseudomonas aeruginosa* and its release by azolectin. *FEMS Microbiol Lett* 1989;51:327–32.

- [13] McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999;12:147-79.
- [14] Stinner DJ, Krueger CA, Masini BD, Wenke JC. Time-dependent effect of chlorhexidine surgical prep. *J Hosp Infect* 2011;79:313-6. doi:10.1016/j.jhin.2011.08.016.
- [15] Hibbard JS. Analyses comparing the antimicrobial activity and safety of current antiseptic agents: a review. *J Infus Nurs* 2005;28:194-207.
- [16] 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. doi:10.1016/S1473-3099(05)70295-4.
- [17] Garibaldi RA. Prevention of intraoperative wound contamination with chlorhexidine shower and scrub. *J Hosp Infect* 1988;11 (Suppl B):5-9.
- [18] Paulson DS. Efficacy evaluation of a 4% chlorhexidine gluconate as a full-body shower wash. *Am J Infect Control* 1993;21:205-9.
- [19] Chlebicki MP, Safdar N, O'Horo JC, Maki DG. Preoperative chlorhexidine shower or bath for prevention of surgical site infection: a meta-analysis. *Am J Infect Control* 2013;41:167-73. doi:10.1016/j.ajic.2012.02.014.
- [20] Hayek LJ, Emerson JM, Gardner AM. A placebo-controlled trial of the effect of two preoperative baths or showers with chlorhexidine detergent on postoperative wound infection rates. *J Hosp Infect* 1987;10:165-72.
- [21] Ayliffe GA, Noy MF, Babb JR, Davies JG, Jackson J. A comparison of pre-operative bathing with chlorhexidine-detergent and non-medicated soap in the prevention of wound infection. *J Hosp Infect* 1983;4:237-44.
- [22] Leigh DA, Stronge JL, Marriner J, Sedgwick J. Total body bathing with "Hibiscrub" (chlorhexidine) in surgical patients: a controlled trial. *J Hosp Infect* 1983;4:229-35.
- [23] Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev* 2015;CD004985. doi:10.1002/14651858.CD004985.pub5.
- [24] Rutter JD, Angiulo K, Macingo DR. Measuring residual activity of topical antimicrobials: is the residual activity of chlorhexidine an artefact of laboratory methods? *J Hosp Infect* 2014;88:113-5. doi:10.1016/j.jhin.2014.06.010.
- [25] Wade JJ, Casewell MW. The evaluation of residual antimicrobial activity on hands and its clinical relevance. *J Hosp Infect* 1991;18 (Suppl B):23-8.
- [26] Chen AF, Wessel CB, Rao N. *Staphylococcus aureus* screening and decolonization in orthopaedic surgery and reduction of surgical site infections. *Clin Orthop Relat Res* 2013;471:2383-99. doi:10.1007/s11999-013-2875-0.
- [27] Rao N, Cannella B, Crosslett LS, Yates AJ, McGough R. A preoperative decolonization protocol for *Staphylococcus aureus* prevents orthopaedic infections. *Clin Orthop Relat Res* 2008;466:1343-8. doi:10.1007/s11999-008-0225-4.
- [28] Bode LGM, Kluytmans JAJW, Wertheim HFL, Bogaers D, Vandembroucke-Grauls CMJE, Roosendaal R, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010;362:9-17. doi:10.1056/NEJMoa0808939.
- [29] Kapadia BH, Zhou PL, Jauregui JJ, Mont MA. Does Preadmission Cutaneous Chlorhexidine Preparation Reduce Surgical Site Infections After Total Knee Arthroplasty? *Clin Orthop Relat Res* 2016;474:1592-8. doi:10.1007/s11999-016-4767-6.
- [30] Edmiston CE, Krepel CJ, Edmiston SE, Spencer M, Lee C, Brown KR, et al. Empowering the surgical patient: a randomized, prospective analysis of an innovative strategy for improving patient compliance with preadmission showering protocol. *J Am Coll Surg* 2014;219:256-64. doi:10.1016/j.jamcollsurg.2014.01.061.
- [31] Kapadia BH, Cherian JJ, Issa K, Jagannathan S, Daley JA, Mont MA. Patient Compliance with Preoperative Disinfection Protocols for Lower Extremity Total Joint Arthroplasty. *Surg Technol Int* 2015;26:351-4.
- [32] 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. doi:10.1016/j.jamcollsurg.2007.12.054.
- [33] Johnson AJ, Daley JA, Zywielski MG, Delanois RE, Mont MA. Preoperative chlorhexidine preparation and the incidence of surgical site infections after hip arthroplasty. *J Arthroplasty* 2010;25:98-102. doi:10.1016/j.arth.2010.04.012.
- [34] Eiselt D. Presurgical skin preparation with a novel 2% chlorhexidine gluconate cloth reduces rates of surgical site infection in orthopaedic surgical patients. *Orthop Nurs* 2009;28:141-5. doi:10.1097/NOR.0b013e3181a469db.
- [35] Zywielski MG, Daley JA, Delanois RE, Naziri Q, Johnson AJ, Mont MA. Advance pre-operative chlorhexidine reduces the incidence of surgical site infections in knee arthroplasty. *Int Orthop* 2011;35:1001-6. doi:10.1007/s00264-010-1078-5.
- [36] Kapadia BH, Jauregui JJ, Murray DP, Mont MA. Does Preadmission Cutaneous Chlorhexidine Preparation Reduce Surgical Site Infections After Total Hip Arthroplasty? *Clin Orthop Relat Res* 2016;474:1583-8. doi:10.1007/s11999-016-4748-9.
- [37] Farber NJ, Chen AF, Bartsch SM, Feigel JL, Klatt BA. No infection reduction using chlorhexidine wipes in total joint arthroplasty. *Clin Orthop Relat Res* 2013;471:3120-5. doi:10.1007/s11999-013-2920-z.
- [38] Wihlborg O. The effect of washing with chlorhexidine soap on wound infection rate in general surgery. A controlled clinical study. *Ann Chir Gynaecol* 1987;76:263-5.
- [39] Larson E. Guideline for use of topical antimicrobial agents. *Am J Infect Control* 1988;16:253-66.
- [40] Lowbury EJ, Lilly HA. The effect of bath on disinfection of surgeons' hands. *Br J Surg* 1974;61:19-21.
- [41] Sistla SC, Prabhu G, Sistla S, Sadasivan J. Minimizing wound contamination in a "clean" surgery: comparison of chlorhexidine-ethanol and povidone-iodine. *Chemotherapy* 2010;56:261-7. doi:10.1159/000319901.
- [42] Saltzman MD, Nuber GW, Gryzlo SM, Marecek GS, Koh JL. Efficacy of surgical preparation solutions in shoulder surgery. *J Bone Joint Surg Am* 2009;91:1949-53. doi:10.2106/JBJS.H.00768.
- [43] Bibbo C, Patel D V, Gehrman RM, Lin SS. Chlorhexidine provides superior skin decontamination in foot and ankle surgery: a prospective randomized study. *Clin Orthop Relat Res* 2005;438:204-8.
- [44] Ostrander R V, Botte MJ, Brage ME. Efficacy of surgical preparation solutions in foot and ankle surgery. *J Bone Joint Surg Am* 2005;87:980-5. doi:10.2106/JBJS.D.01977.
- [45] Paocharoen V, Mingmalairak C, Apisarnthanarak A. Comparison of surgical wound infection after preoperative skin preparation with 4% chlorhexidine [correction of chlorhexidine] and povidone iodine: a prospective randomized trial. *J Med Assoc Thai* 2009;92:898-902.
- [46] Swenson BR, Hedrick TL, Metzger R, Bonatti H, Pruett TL, Sawyer RG. Effects of preoperative skin preparation on postoperative wound infection rates: a prospective study of 3 skin preparation protocols. *Infect Control Hosp Epidemiol* 2009;30:964-71. doi:10.1086/605926.
- [47] 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. doi:10.1056/NEJMoa0810988.
- [48] Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2015;CD003949. doi:10.1002/14651858.CD003949.pub4.
- [49] Parviz J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J* 2013;95B:1450-2. doi:10.1302/0301-620X.95B11.33135.
- [50] HICPAC. Healthcare Infection Control Practices Advisory Committee (HICPAC) - Meeting Summary Report. 2013.
- [51] Widmer AF. Surgical hand hygiene: scrub or rub? *J Hosp Infect* 2013;83 Suppl 1:S35-9. doi:10.1016/S0195-6701(13)60008-0.
- [52] Dahl J, Wheeler B, Mukherjee D. Effect of chlorhexidine scrub on postoperative bacterial counts. *Am J Surg* 1990;159:486-8.
- [53] Parienti JJ, Thibon P, Heller R, Le Roux Y, von Theobald P, Bensadoun H, et al. Hand-rubbing with an aqueous alcoholic solution vs traditional surgical hand-scrubbing and 30-day surgical site infection rates: a randomized equivalence study. *JAMA* 2002;288:722-7.
- [54] Tanner J, Dumville JC, Norman G, Fortnam M. Surgical hand antisepsis to reduce surgical site infection. *Cochrane Database Syst Rev* 2016;CD004288. doi:10.1002/14651858.CD004288.pub3.
- [55] Odum SM, Fehring TK, Lombardi A V, Zmistowski BM, Brown NM, Luna JT, et al. Irrigation and debridement for periprosthetic infections: does the organism matter? *J Arthroplasty* 2011;26:114-8. doi:10.1016/j.arth.2011.03.031.
- [56] Owens BD, White DW, Wenke JC. Comparison of irrigation solutions and devices in a contaminated musculoskeletal wound survival model. *J Bone Joint Surg Am* 2009;91:92-8. doi:10.2106/JBJS.G.01566.
- [57] Conroy BP, Anglen JO, Simpson WA, Christensen G, Phaup G, Yeager R, et al. Comparison of castile soap, benzalkonium chloride, and bacitracin as irrigation solutions for complex contaminated orthopaedic wounds. *J Orthop Trauma* 1999;13:332-7.
- [58] Azzam KA, Seeley M, Ghanem E, Austin MS, Purtill JJ, Parviz J. Irrigation and debridement in the management of prosthetic joint infection: traditional indications revisited. *J Arthroplasty* 2010;25:1022-7. doi:10.1016/j.arth.2010.01.104.
- [59] FLOW Investigators, Bhandari M, Jeray KJ, Petrison BA, Devereaux PJ, Heels-Ansdell D, et al. A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds. *N Engl J Med* 2015;373:2629-41. doi:10.1056/NEJMoa1508502.
- [60] Anglen JO. Comparison of soap and antibiotic solutions for irrigation of lower-limb open fracture wounds. A prospective, randomized study. *J Bone Joint Surg Am* 2005;87:1415-22. doi:10.2106/JBJS.D.02615.
- [61] Schwechter EM, Folk D, Varshney AK, Fries BC, Kim SJ, Hirsh DM. Optimal irrigation and debridement of infected joint implants: an in vitro methicillin-resistant *Staphylococcus aureus* biofilm model. *J Arthroplasty* 2011;26:109-13. doi:10.1016/j.arth.2011.03.042.
- [62] Smith DC, Maiman R, Schwechter EM, Kim SJ, Hirsh DM. Optimal Irrigation and Debridement of Infected Total Joint Implants with Chlorhexidine Gluconate. *J Arthroplasty* 2015;30:1820-2. doi:10.1016/j.arth.2015.05.005.
- [63] van Meurs SJ, Gawlitta D, Heemstra KA, Poolman RW, Vogely HC, Kruijff MC. Selection of an optimal antiseptic solution for intraoperative irrigation: an in vitro study. *J Bone Joint Surg Am* 2014;96:285-91. doi:10.2106/JBJS.M.00313.
- [64] Tejwani NC, Immerman I. Myths and legends in orthopaedic practice: are we all guilty? *Clin Orthop Relat Res* 2008;466:2861-72. doi:10.1007/s11999-008-0458-2.
- [65] Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H. Topical silver for preventing wound infection. *Cochrane Database Syst Rev* 2010;CD006478. doi:10.1002/14651858.CD006478.pub2.
- [66] Chowdhry M, Chen AF. Wound dressings for primary and revision total joint arthroplasty. *Ann Transl Med* 2015;3:268. doi:10.3978/j.issn.2305-5839.2015.09.25.
- [67] Carty N, Wibaux A, Ward C, Paulson DS, Johnson P. Antimicrobial activity of a novel adhesive containing chlorhexidine gluconate (CHG) against the

- resident microflora in human volunteers. *J Antimicrob Chemother* 2014;69:2224-9. doi:10.1093/jac/dku096.
- [68] 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: a meta-analysis*. *Crit Care Med* 2014;42:1703-13. doi:10.1097/CCM.0000000000000319.
- [69] Wu SC, Crews RT, Zelen C, Wrobel JS, Armstrong DG. Use of chlorhexidine-impregnated patch at pin site to reduce local morbidity: the ChIPPS Pilot Trial. *Int Wound J* 2008;5:416-22. doi:10.1111/j.1742-481X.2007.00368.x.
- [70] Obermeier A, Schneider J, Wehner S, Matl FD, Schieker M, von Eisenhart-Rothe R, et al. Novel high efficient coatings for anti-microbial surgical sutures using chlorhexidine in fatty acid slow-release carrier systems. *PLoS One* 2014;9:e101426. doi:10.1371/journal.pone.0101426.
- [71] Apisarnthanarak A, Singh N, Bandong AN, Madriaga G. Triclosan-coated sutures reduce the risk of surgical site infections: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015;36:169-79. doi:10.1017/ice.2014.22.
- [72] Wang J-T, Sheng W-H, Wang J-L, Chen D, Chen M-L, Chen Y-C, 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. doi:10.1093/jac/dkn208.
- [73] Sheng W-H, Wang J-T, Lauderdale T-L, Weng C-M, Chen D, Chang S-C. Epidemiology and susceptibilities of methicillin-resistant *Staphylococcus aureus* in Taiwan: emphasis on chlorhexidine susceptibility. *Diagn Microbiol Infect Dis* 2009;63:309-13. doi:10.1016/j.diagmicrobio.2008.11.014.
- [74] Kampf G, Jarosch R, Rüden H. Limited effectiveness of chlorhexidine based hand disinfectants against methicillin-resistant *Staphylococcus aureus* (MRSA). *J Hosp Infect* 1998;38:297-303.
- [75] 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. doi:10.1093/jac/dks284.
- [76] Zhang M, O'Donoghue MM, Ito T, Hiramatsu K, Boost M V. Prevalence of antiseptic-resistance genes in *Staphylococcus aureus* and coagulase-negative staphylococci colonising nurses and the general population in Hong Kong. *J Hosp Infect* 2011;78:113-7. doi:10.1016/j.jhin.2011.02.018.
- [77] Cookson BD, Bolton MC, Platt JH. Chlorhexidine resistance in methicillin-resistant *Staphylococcus aureus* or just an elevated MIC? An in vitro and in vivo assessment. *Antimicrob Agents Chemother* 1991;35:1997-2002.
- [78] 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. doi:10.1093/jac/dkm395.
- [79] Karpanen TJ, Worthington T, Conway BR, Hilton AC, Elliott TSJ, Lambert PA. Penetration of chlorhexidine into human skin. *Antimicrob Agents Chemother* 2008;52:3633-6. doi:10.1128/AAC.00637-08.
- [80] Khan RA, Kazi T, O'Donohoe B. Near fatal intra-operative anaphylaxis to chlorhexidine—is it time to change practice? *BMJ Case Rep* 2011; doi:10.1136/bcr.09.2009.2300.
- [81] Dyer JE, Nafie S, Mellon JK, Khan MA. Anaphylactic reaction to intraurethral chlorhexidine: sensitisation following previous repeated uneventful administration. *Ann R Coll Surg Engl* 2013;95:e105-6. doi:10.1308/003588413X13629960047597.
- [82] Sijbesma T, Röckmann H, van der Weegen W. Severe anaphylactic reaction to chlorhexidine during total hip arthroplasty surgery. A case report. *Hip Int* 2011;21:630-2. doi:10.5301/HIP.2011.8644.
- [83] Mariotti AJ, Rumpf DA. Chlorhexidine-induced changes to human gingival fibroblast collagen and non-collagen protein production. *J Periodontol* 1999;70:1443-8. doi:10.1902/jop.1999.70.12.1443.
- [84] Arabaci T, Türkez H, Çanakçı CF, Özgöz M. Assessment of cytogenetic and cytotoxic effects of chlorhexidine digluconate on cultured human lymphocytes. *Acta Odontol Scand* 2013;71:1255-60. doi:10.3109/00016357.2012.757646.
- [85] Patel P, Ide M, Coward P, Di Silvio L. The effect of a commercially available chlorhexidine mouthwash product on human osteoblast cells. *Eur J Prosthodont Restor Dent* 2006;14:67-72.
- [86] Douw CM, Bulstra SK, Vandenbroucke J, Geesink RG, Vermeulen A. Clinical and pathological changes in the knee after accidental chlorhexidine irrigation during arthroscopy. Case reports and review of the literature. *J Bone Joint Surg Br* 1998;80:437-40.
- [87] Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty* 2012;27:61-5.e1. doi:10.1016/j.arth.2012.02.022.
- [88] 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. doi:10.1086/657134.
- [89] Kapadia BH, Johnson AJ, Issa K, Mont MA. Economic evaluation of chlorhexidine cloths on healthcare costs due to surgical site infections following total knee arthroplasty. *J Arthroplasty* 2013;28:1061-5. doi:10.1016/j.arth.2013.02.026.