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Research Review

Evaluation of the role of povidone-iodine in the prevention of surgical site infections

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ABSTRACT

Background: The occurrence of surgical site infections (SSIs) is associated with increased risk of mortality, development of other infections, and the need for reintervention, posing a significant health burden. The aim of this review was to examine the current data and guidelines around the use of antiseptic povidone-iodine (PVP-I) for the prevention of SSIs at each stage of surgical intervention.
Methods: A literature search for selected key words was performed using PubMed. Additional papers were identified based on author expertise.
Results: Scientific evidence demonstrates that PVP-I can be used at every stage of surgical intervention: preoperative, intraoperative, and postoperative. PVP-I is one of the most widely used antiseptics on healthy skin and mucous membranes for preoperative surgical site preparation and is associated with a low SSI rate. For intraoperative irrigation, aqueous PVP-I is the recommended agent and has been demonstrated to decrease SSIs in a range of surgical settings, and for postoperative wound healing, there is a growing body of evidence to support the use of PVP-I.
Conclusions: There is a need for more stringent study designs in clinical trials to enable meaningful comparisons between antiseptic agents, particularly for preoperative skin preparation. The use of a single agent (PVP-I) at each stage of surgical intervention could potentially provide advantages, including economic benefits, over agents that can only be used at discrete stages of the surgical procedure.
Key message: Evidence supports the use of PVP-I at all stages of surgical intervention, from preoperative measures (including skin preparation, preoperative washing, and nasal decolonization) to intraoperative irrigation, through to postoperative wound management. However, there is a need for more stringent study designs in clinical trials to enable meaningful comparisons between antiseptic agents, particularly for preoperative skin preparation.

Contents

Abbreviations: CDC, Centers for Disease Control and Prevention; CHX, Chlorhexidine; CRBSI, Catheter-related bloodstream infection; ESKAPE, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.*; FDA, Food and Drug Administration; IDSA, Infectious Diseases Society of America; LRF, Logarithmic reduction factors; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *S. aureus*; PVP-I, Povidone-iodine; SmPC, Summary of Product Characteristics; SSI, Surgical site infection; TGF-β, Transforming growth factor beta; US, United States; WHO, World Health Organization.

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Introduction

The clinical and economic impact of surgical site infections. Surgical site infections (SSIs), defined as postoperative infection occurring within 30 days of a surgical procedure (or within 1 year for permanent implants), are one of the most frequent types of healthcare-associated infections [1,2]. The occurrence of SSIs is associated with increased risk of mortality, reintervention, organ-space infection, and other healthcare-associated infections [3].

Patients in low-income countries have an increased risk of SSIs *versus* those in high-income countries; however, the incidence of SSIs in middle- and high-income countries is still notable (14 % and 9 %, respectively, in a study of patients undergoing elective or emergency gastrointestinal resection) [3]. This poses a significant healthcare burden: in an England-based study, SSIs were responsible for 4694 hospital bed-days over 2 years, which is the equivalent of 6.4 beds per day [4]. Additionally, the United States (US) Centers for Disease Control and Prevention (CDC) guidelines evaluated the mean cost of SSI treatment to range from US $10,443–US $25,546 per SSI [5]. However, it has been suggested that the economic burden associated with SSIs has been underestimated due to under-reporting of the true rate of SSIs [6].

As antibiotic resistance is one of the biggest threats to global health today [7], the use of antiseptics may be preferable to antibiotics for the prevention of SSIs, thanks to their lower tendency to induce bacterial resistance and cross-resistance and their broader spectrum of antimicrobial activity [8]. Some antiseptics, for example specific povidone-iodine (PVP-I)-based products, can be used at all stages of surgical intervention, from preoperative measures including skin preparation, preoperative washing, and nasal methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization, to intraoperative irrigation, and ultimately postoperative management of surgical wounds [9]. This could potentially provide an economic advantage over the use of multiple different agents that can only be used at discrete stages of the surgical procedure. Future health economics and outcomes studies would be beneficial to investigate these potential economic advantages, particularly in low- and middle-income countries.

Properties and activity of commonly used antiseptics. There are several major classes of antiseptics, including biguanides (eg, chlorhexidine [CHX]), iodine derivatives (eg, PVP-I), chlorine derivatives (eg, sodium hypochlorite), and alcohols. Each antiseptic has a different mechanism of action, antimicrobial spectrum, and resistance profile. Table 1 shows the properties of two of the most commonly used antiseptics, CHX and PVP-I.

Antimicrobial activity can be influenced by physical factors (eg, pH of the skin, ambient temperature, interfering organic materials), chemical factors (eg, antiseptic concentration), microbiological factors (quantity and nature of microorganisms), and mode of application [10,11].

Numerous studies have been published investigating the antimicrobial activity of antiseptic agents [12–17]. *In vitro*, 0.05 % and 0.1 % PVP-I were microbicidal against methicillin-sensitive *S. aureus* (MSSA) and MRSA within 20 s [8,17], while 0.05 % CHX required between 2 and 20–30 min to kill the various strains of MSSA and MRSA [8,16]. Most of the data on antimicrobial activity have been derived from *in vitro* studies using suspensions of microbial cells [12]; however, phase 2/step 2 studies have been proposed as a progression from cell suspension tests [18]. In one such study, the activity of a variety of antiseptics was assessed *in vitro* in the presence of organic material. The antiseptics were tested against microbial test suspensions pre-dried on a metal carrier; this method was suggested to be more representative of antiseptic treatment of a wound than cell suspension tests [18]. Using this method, the effect of organic material on PVP-I, CHX, polyhexanide, and

Table 1
Properties of chlorhexidine and povidone-iodine [130].

	Mechanism of action	Bactericidal activity	Antimicrobial spectrum	Resistance profile
CHX	Alters the permeability of the microorganism cell membrane and causes leakage of cellular constituents [128]	Effective against most ESKAPE pathogens (variable/limited activity against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) [129]; less effective than PVP-I in the presence of organic material [18,129]; less effective at eradicating *Acinetobacter baumannii*, *Escherichia coli*, MRSA, and *P. aeruginosa* in biofilms than free-form bacteria; higher efficacy in young *versus* mature biofilms [129]	Broad spectrum of activity against Gram-positive bacteria. Incomplete spectrum of activity against Gram-negative bacteria, fungi, and viruses. No activity against spores [8]	CHX resistance observed in *Staphylococcus epidermidis*, *A. baumannii*, and *Mycobacterium abscessus*. Cross-resistance to colistin, vancomycin, and daptomycin[a] has been observed [130–135]
PVP-I	Penetrates microorganisms and oxidizes key proteins, nucleotides, and fatty acids, leading to cell death [66]	Effective against all ESKAPE pathogens [129]; shortest time to efficacy against *Staphylococcus aureus*, *Enterococcus faecium*, and *P. aeruginosa* in the presence of blood (compared with CHX, polyhexanide, and octenidine) [18,129]; highly effective at eradicating biofilms, including MRSA, *K. pneumoniae*, *P. aeruginosa*, and *Candida albicans* [129]	Broad spectrum of activity against Gram-positive bacteria, Gram-negative bacteria, fungi, viruses, and spores [8]	No observed antimicrobial resistance/cross-resistance [136,137]

CHX, chlorhexidine; ESKAPE, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, Enterobacter spp.; MRSA, methicillin-resistant *Staphylococcus aureus*; PVP-I, povidone-iodine.
[a] Daptomycin has activity against most Gram-positive pathogens, including vancomycin-resistant enterococci and MRSA [138].

octenidine activity was tested. PVP-I had the shortest time to efficacy (≤30 min) against *S. aureus*, *Enterococcus faecium,* and *Pseudomonas aeruginosa*, even in the presence of blood. Octenidine also displayed rapid activity: its efficacy against *S. aureus* was similar to PVP-I; however, against *E. faecium* and *P. aeruginosa*, octenidine required longer exposure times ranging between 30 min and 10 h. Conversely, the effects of CHX and polyhexanide were generally less rapid (ranging from 5 min to >24 h depending on the species and presence of bioburden) [18].

While *in vitro* activity studies can be informative, it should be noted that environmental laboratory factors can influence observations [19]. Selection of the most appropriate antiseptic in real-world practice should therefore be based on clinical data and evidence-based guidelines.

Methods

This narrative review was guided using information derived from a virtual focus meeting, attended by the authors (October 2021), and a subsequent literature search of the PubMed database using selected search terms. Search terms were chosen based on discussions during the focus meeting, and no date restrictions were included in the searches. Additional papers were identified based on authors' expertise. Only papers deemed directly relevant were included in this review.

Results

Antiseptic skin agents in the prevention of SSIs: current scientific data. SSI prevention is complex and requires the integration of preventive measures before, during, and after surgery [2]. Here, we discuss evidence for the most appropriate use of antiseptic preparations at each stage of surgical intervention.

i) Preoperative antisepsis

Guideline Recommendations for the Use of Antiseptics in Preoperative Skin Preparation

PVP-I is one of the most widely used antiseptics for the prevention of SSIs, and is associated with a low SSI rate [20]. However, in 2016, the World Health Organization (WHO) published new guidelines: considering the available evidence, the WHO Guidelines Development Group recommended the use of an alcohol-based antiseptic solution based on CHX for surgical site preparation in patients undergoing surgical procedures [21]. This recommendation was sustained in the 2018 WHO guidelines update (strong recommendation, low-to-moderate quality of evidence) [2].

The meta-analysis that contributed to the WHO recommendation, concluding that alcoholic CHX is beneficial in reducing SSI rates compared with alcoholic PVP-I, was based on studies rated as low-quality evidence [2]. Furthermore, discrepancies in the trials concerned have led to questions over the validity of the recommendation. These discrepancies included the comparison of alcoholic CHX *versus* aqueous PVP-I, small sample sizes, and antiseptics used in the trials having unknown or suboptimal alcohol concentrations [20,22,23]. Furthermore, the body of evidence supporting the WHO recommendation focused on adult patients and no studies were available in the pediatric population. Therefore, the effectiveness of alcoholic CHX is not proven for pediatric patients [2].

In a repeated meta-analysis by Maiwald et al. after an updated systematic literature search and exclusion of the trials using antiseptics with inadequate or unknown alcohol concentrations, CHX was no longer shown to be superior to PVP-I for preventing SSIs, indicating that the WHO recommendation was premature [20]. The authors of the original meta-analysis cited by the WHO have published a response to this criticism, in which they stand by the findings of their study but acknowledge that the availability of alcoholic CHX-based preparations remains limited and can be an additional cost in developing countries [24].

Other organizations, including the international Orthopaedic Research Society [25], the international Institute for Healthcare Improvement [26], the US CDC [5], and the French Society of Hospital Hygiene [27], do not align with the WHO's recommendation, and continue to recommend alcohol-based antisepsis with either CHX or PVP-I. This more neutral and balanced position between the two agents, recommending the use of alcohol-based antisepsis with either CHX or PVP-I, may be more appropriate.

Current scientific data on antiseptics for preoperative skin preparation

Despite cumulative evidence in favor of alcoholic CHX [28–31], the most appropriate preoperative skin antiseptic has not yet been definitively established. Studies publishing evidence in favor of alcoholic CHX *versus* PVP-I as a skin antiseptic have received criticism due to inconsistencies in study design [22,23,32].

One of these inconsistencies was the use of alcoholic *versus* aqueous preparations: in a 2010 meta-analysis [28] and a separate systematic review of the same year [31], alcoholic CHX preparations were directly compared with aqueous PVP-I in the majority of the evaluated trials [22,23]. However, alcohol alone was described by the CDC as “the most effective and rapid-acting skin antiseptic” [33] and alcoholic PVP-I is associated with a lower incidence of catheter colonization and infection than aqueous PVP-I [34]; thus, comparing alcoholic CHX with aqueous PVP-I is not an appropriate comparison [22,23].

Another inconsistency, exemplified by the CLEAN [29] and CLEAN 3 [30] studies, was application technique. These studies compared the efficacy of alcoholic CHX with alcoholic PVP-I prior to catheter insertion and concluded that alcoholic CHX was associated with a lower incidence of catheter-related infections [29,30]. In both studies, alcoholic CHX applied with a pre-filled applicator using the back-and-forth friction technique was compared with alcoholic PVP-I applied with a compress using the concentric circles technique [29,30]. While the Summary of Product Characteristics (SmPC) for alcoholic CHX specifically recommends its application using a back-and-forth technique [35], the PVP-I SmPC does not explicitly recommend the concentric circles technique used in CLEAN and CLEAN 3 [36]. Historically, skin antiseptics have been applied using the concentric circles technique; however, there is no guarantee that this method results in aseptic skin, and no evidence was found in the literature to support this technique [37,38]. Applying friction, as in the back-and-forth friction technique (but not in the concentric circles technique), is beneficial for skin preparation, as it ensures cleaning through the top five dermal layers of skin, which harbor a large proportion of the skin's bacterial load, and removes most of the bacteria from this region [37,38]. Furthermore, in a randomized, open-label study, a significantly greater reduction in colony-forming unit count was achieved when applying PVP-I using the back-and-forth friction technique *versus* the concentric circles technique to back skin of healthy volunteers [39]. Therefore, given the potentially beneficial effect of the back-and-forth friction technique compared with the concentric circles technique, the use of different methods of antiseptic application in the CLEAN studies could have influenced the conclusions [37,38].

Furthermore, the use of a pre-filled applicator with CHX could have had greater antiseptic activity compared with the use of a compress with PVP-I; a single-use pre-filled applicator could result in greater consistency in the volume of antiseptic used and less heterogeneity in the way it was applied by healthcare professionals, as well as offering reduction of the risk of cross-contamination during antiseptic application [38].

Finally, a further factor in study design that has received criticism relates to study endpoints: the CLEAN 3 primary outcome was a composite endpoint of “catheter-related infectious complications”, incorporating catheter colonization, local infection, and catheter-related bloodstream infection (CRBSI). However, catheter colonization, while appropriate for small exploratory pilot studies, has been suggested to be inappropriate for establishing definite patient-oriented benefit or harm of an intervention [30,32]. In a meta-

analysis, catheter colonization showed poor agreement with CRBSI at the individual patient level and poor "capture" at the study level ("capture" was defined as the degree to which treatment effects on CRBSI were captured by the surrogates) [32]. The authors concluded that, although catheter colonization and CRBSI were correlated, antiseptic effects on CRBSI may not be adequately captured by catheter colonization [32]. As such, the primary outcome in the large CLEAN 3 trial may not be appropriate for definitively determining the patient-oriented benefit or harm of the antiseptics tested.

Conversely, evidence has been published in favor of alcoholic PVP-I *versus* alcoholic CHX preparations for the prevention of SSIs in various surgical settings; for example, Dörfel et al. demonstrated that on the shoulder region of healthy volunteers, alcoholic PVP-I showed a certain degree of benefit *versus* alcoholic CHX in reducing aerobic flora counts, but more substantial benefits in reducing anaerobic flora counts [40]. One of the main constituents of anaerobic flora is *Cutibacterium acnes* (formerly *Propionibacterium acnes*) [40]. *C. acnes* is frequently detected as a cause of SSIs, particularly in prosthetic joint infections and most frequently in shoulder prosthetic joint infections [41,42]. In addition, *C. acnes* can be involved in infections after hip and knee joint replacements [43], polyurethane-coated breast implants [44], and various other implants [45]. *C. acnes* is primarily located in the deeper layers of the skin, in hair follicles, and pilo-sebaceous glands; therefore, the findings of Dörfel et al. indicate that alcoholic PVP-I may be a promising option for preoperative antisepsis on skin with a high density of sebaceous glands [40]. Indeed, compared with alcoholic CHX, alcoholic PVP-I is hypothesized to have a greater antimicrobial effect against the deep resident skin flora due to the capacity for iodine to penetrate the deeper layers of the skin [40]. This hypothesis is based on experiments with excised human skin in diffusion chambers, showing that aqueous CHX penetrates relatively poorly into deep skin layers [46], while iodine released from PVP-I can pass through the skin in clinically relevant amounts [47].

Further evidence in favor of alcoholic PVP-I includes a study in patients undergoing hip or knee arthroplasties. Patients were randomized to receive surgical site preparation with either alcoholic CHX or alcoholic iodine. There were increased odds of SSI in the alcoholic CHX group compared with the alcoholic iodine group: 3.1 % *versus* 1.0 %, respectively; odds ratio (95 % confidence interval): 3.06 (1.26–7.46); $P = 0.014$ [48]. In this study, although the original trial protocol stipulated 10 % PVP-I (with 1 % available iodine) in 70 % alcohol, the protocol was amended to 1 % iodine in 70 % ethanol, based on institutional preference and experience [48].

Importantly, aqueous-based iodine solutions, such as PVP-I, are one of the few antiseptics that can be safely used on mucous membrane surfaces and therefore should be the antiseptic of choice for procedures such as transurethral and transvaginal surgery [49]. Any alcohol-based solutions should not be applied to mucous membranes because of the risk of burns [49,50].

Thus, due to the conflicting evidence summarized above, practitioners may consider other characteristics (eg, safety and cost) when selecting a preoperative antiseptic agent.

Safety

With regards to safety, while all antiseptics have irritant properties [51], the WHO guidelines for SSI prevention note that CHX may cause skin irritation, delayed reactions such as contact dermatitis and photosensitivity, and, in some very rare cases, hypersensitivity reactions such as anaphylactic shock [2]. In a position statement on anaphylaxis guidance, the World Allergy Organization identified "disinfectants like CHX" as "novel substances inducing anaphylaxis" [52], while a review by Rose et al. stated that CHX is a "known irritant in high concentrations" [53]. Irritant contact dermatitis with CHX causing localized transient irritation, which disappears spontaneously on avoidance, has been reported in doctors and other healthcare workers [53]. Furthermore, spillage of CHX into the eye when used as an antiseptic for facial procedures, such as aesthetic injections, can lead to significant chemical burns in the form of keratitis [54–56]. CHX, when used as an antiseptic eardrop, has also been shown to damage the middle ear, with the potential to cause permanent sensorineural deafness if it penetrates a perforated ear drum [56].

When the safety of alcoholic CHX ($n = 1044$) and alcoholic PVP-I ($n = 1011$) was directly compared in the CLEAN study, skin reactions of all severity were more frequent with alcoholic CHX than with alcoholic PVP-I (17.5 % *vs* 14.4 %, respectively; $P = 0.011$) [29]. Severe skin reactions were also more frequent with alcoholic CHX *versus* alcoholic PVP-I (2.6 % *vs* 0.7 %, respectively; $P = 0.002$), and led to CHX discontinuation in two of the 1044 patients [29]. Conversely, in the CLEAN 3 study ($N = 989$), minor skin reactions were uncommon (1.6 % overall), with no significant difference between alcoholic CHX and alcoholic PVP-I (1.8 % and 1.4 %, respectively; adjusted relative risk [95 % confidence interval]: 1.06 [0.77–1.35]) [30]. There were no severe skin reactions reported [30].

Cost

PVP-I dressings and solutions are relatively inexpensive compared with other antimicrobial therapies [57]. CHX is more expensive than PVP-I, potentially leading to issues with affordability in low-income countries [20]. The authors of the meta-analysis cited by the WHO acknowledged that the availability of alcoholic CHX-based preparations remains limited and could be an additional cost in developing countries [24]. Furthermore, it has been suggested that dressings that change color (eg, iodine dressings containing 10 % PVP-I, which decolor as the iodine is absorbed) may be more cost-effective in that they provide an indicator of how frequently dressings should be changed. This may prevent unnecessary dressing changes and save both dressing costs and nursing time [57,58]. Based on this, the cost of antiseptic preparations may impact clinical decisions surrounding antiseptic agent.

Preoperative washing

Preoperative washing with an antiseptic agent may also be a beneficial measure for SSI prevention. The WHO recommends that either a plain or antimicrobial soap may be used by patients for bathing or showering prior to surgery to ensure that the skin is as clean as possible and to reduce the bacterial load, especially at the site of incision [2]. At the time of publishing the guidelines, the only evidence available for preoperative washing with an antimicrobial soap was of moderate quality and showed that preoperative bathing with antimicrobial soap containing CHX had neither a positive nor negative impact on reducing the rate of SSIs compared with plain soap. As no other studies were available, either plain or antimicrobial soap was recommended [2]. In a recent modeling study in France using a healthcare infection database, preoperative showering with antimicrobial soap was predicted to prevent 209 SSIs per year compared with no antimicrobial soap, leading to a potential saving of €632,210 per year based on the price of PVP-I [59].

Preoperative nasal decolonization

Nasal carriage of S. aureus at the time of surgery has been shown to increase the risk of SSIs [60,61]. Furthermore, positivity for MRSA is associated with higher rates of mortality following infection compared with methicillin-susceptible *S. aureus* [62]. Thus, screening and decolonization of *S. aureus*in carriers prior to surgery is a promising method for reducing surgical site staphylococcal infections and their associated risks. The WHO guidelines recommend intranasal applications of mupirocin 2 % ointment with or without CHX body wash for patients with known nasal carriage of *S. aureus* who are undergoing cardiothoracic or orthopedic surgery; patients with known *S. aureus* carriage undergoing other types of surgery should also be considered for this regimen [2].

However, mupirocin is expensive and is not currently universally available [63]. Additionally, there are growing concerns about decolonization failures due to mupirocin resistance [64]. In particular, the effect of CHX body wash in combination with mupirocin on the development of resistance is unknown. In an 8-year surveillance study, 1.8 % of the nasal MRSA isolates tested contained both CHX- and mupirocin-

resistance determinants. Additionally, MRSA isolates positive for qacA/B (CHX tolerance genes) were more likely to be mupirocin-resistant than MRSA isolates negative for qacA/B (ie, CHX-susceptible isolates) (25.0 % *vs* 5.6 %, respectively; $P = 0.003$) [65]. While this may suggest that the use of CHX and mupirocin regimens could lead to selection of co-resistant strains, further study is required to confirm this hypothesis.

Due to these concerns over mupirocin, several studies have investigated the use of intranasal PVP-I solution for preoperative nasal decolonization [66–70]. Preoperative intranasal PVP-I has been shown to have similar efficacy to intranasal mupirocin in preventing SSI in patients undergoing orthopedic surgery, with or without screening for MRSA [67,68]. Patients who applied mupirocin were also more likely to report headache, rhinorrhea, congestion, and sore throat than those who applied PVP-I [67]. In a randomized controlled trial in patients with positive nasal cultures for MRSA, single-dose application of 10 % PVP-I to both nasal vestibules was associated with a statistically significant reduction in mean MRSA concentrations at 1 and 6 h after dosing compared with the saline control ($P < 0.050$), but not at 12 or 24 h. These results suggest that PVP-I may be effective for short-term suppression of *S. aureus* during the perioperative period [69]. Furthermore, one study showed significantly lower SSI rates in patients using topical intranasal PVP-I combined with CHX-impregnated wash cloths and CHX oral rinse compared with those not using these measures [70].

ii) Intraoperative wound irrigation

The WHO, CDC, and Infectious Diseases Society of America (IDSA) recommend irrigation of the incisional wound with an aqueous PVP-I solution before closure to prevent SSIs [2,5,71]. This is particularly recommended in clean and clean-contaminated wounds (ie, wounds showing no signs of infection that may or may not involve repairing or removing an internal organ) [2].

A decrease in SSIs has been reported when diluted aqueous PVP-I is used for wound irrigation in a range of surgical settings, including craniotomy, cesarean delivery, breast surgery, and intraperitoneal irrigation during laparotomy and spinal surgery [72–79]. Conversely, for knee and hip arthroplasties, there is conflicting evidence both in favor and against the use of aqueous PVP-I for wound irrigation [80–83]; for example, in a systematic review and meta-analysis including seven studies and 31,213 patients undergoing total joint arthroplasty, Kim et al. found no difference in postoperative infection rates between patients who underwent PVP-I lavage before wound closure *versus* those without PVP-I lavage [81]. However, in a retrospective study of 31,331 total joint arthroplasty cases between 2009 and 2019, dilute PVP-I irrigation was associated with a 2.34-times lower rate of periprosthetic joint infection compared with saline (0.6 % *vs* 1.3 %, respectively). Using multiple regression analysis, this reduction was statistically significant ($P < 0.001$) [83].

In breast augmentation surgery, the US Food and Drug Administration (FDA) placed a ban on the use of PVP-I for pocket irrigation in 2000, due to the suggestion of a possible degradative effect on the silicone elastomer shell [79]. However, the evidence that led to this decision was subsequently questioned [84]. Following the FDA ban, Zambacos et al. published an *in vitro* experiment which showed that PVP-I had no significant effect on the tensile strength of the silicone elastomer shell after 4 weeks of incubation, when compared with saline [85]. Several further studies have shown no structural effect of PVP-I on breast implants; in fact, a significant decrease in the incidence of capsular contracture has been observed with the use of PVP-I [84]. In 2017, the FDA implemented a change in the 'Directions for Use' for one of the implant brands that removed the ban on PVP-I use in breast augmentation, which is widely thought will benefit patients through reducing the risk of bacterial contamination of implant surfaces [79,86].

Although aqueous PVP-I is the recommended agent for wound irrigation according to the WHO, CDC, and IDSA guidelines, other irrigation preparations, including 0.9 % saline, castile soap, antibiotic solutions, and antiseptics like hydrogen peroxide, have been proposed in the literature [87]. In a study into surgical site irrigation during total hip or knee arthroplasties, no significant difference was seen in infection rates between the CHX irrigation protocol and protocols using dilute PVP-I (for total hip arthroplasty) or 0.9 % saline (for total knee arthroplasty) [87].

For orthopedic surgery, the chondrolytic effects of antiseptics must also be taken into consideration when selecting the most appropriate agent for irrigation. Intra-articular irrigation with even dilute concentrations of CHX for short periods of time can have toxic effects on collagen-producing cells and might result in delayed wound healing [88]. Additionally, 1 min exposure to 0.05 % CHX *in vitro* significantly altered the metabolism of osteoarthritic cartilage, but not non-osteoarthritic cartilage, and prolonged exposure for 1 h markedly affected the metabolism of both types of cartilage [89]. Several case reports have demonstrated that exposure of human articular cartilage to CHX for prolonged periods or at high concentrations results in severe chondrolysis and subsequent joint damage [90–92].

Treatment with polyhexanide, hydrogen peroxide, or taurolidine also induces cell death of human chondrocytes *in vitro* [93]. However, there is conflicting evidence regarding the chondrolytic effects of aqueous PVP-I: in an *in vitro* study, bovine cartilage explants were exposed to different concentrations of PVP-I for 1, 3, or 6 min. Aqueous PVP-I solution at all tested concentrations (0.35 %, 1.40 %, 3.50 %, and 5.00 %) also had a chondrotoxic effect on the superficial cartilage layer when used for longer than 1 min [94]. Conversely, in bovine sesamoid bones *in vitro*, aqueous PVP-I had no negative feedback on cartilage metabolism and actually stimulated chondrocyte metabolism [95]. Further research is needed to determine the chondrolytic effects and associated risks of each antiseptic agent to further facilitate the selection of the most appropriate agent for wound irrigation, particularly in orthopedic surgery.

Antisepsis for preventing biofilm-associated infections

Biofilms are an important consideration across all surgical and wound care settings. It has been reported that at least 80 % of bacterial infections are associated with biofilms [96], and many of the microbial populations associated with SSIs have been observed to exist primarily within a biofilm matrix [97]. Biofilms can promote bacterial survival in the presence of antimicrobial therapies and delay wound healing [98].

Intraoperative irrigation is a suitable method to prevent the formation of biofilms during surgery [99]. Furthermore, the World Union of Wound Healing Societies 2016 Position Document recognizes iodine as a suitable antimicrobial agent to prevent biofilms, as well as acetic acid, honey, polyhexanide, and silver [100]. The efficacy of aqueous PVP-I in eradicating biofilms has been described in numerous *in vitro* studies [101–109] and has been extensively reviewed [110,111]. The *in vitro* efficacy of PVP-I against *Staphylococcus epidermidis* and *S. aureus* growth was demonstrated by Oduwole et al., as was the inhibition of staphylococcal biofilm formation at sub-inhibitory concentrations of PVP-I (low concentrations of antiseptics at which biofilm development can be triggered) [107]. Additionally, low-dose (0.25 %) PVP-I *in vitro* completely eliminated established biofilms of multi-drug resistant *S. aureus*, *Klebsiella pneumoniae*, *P. aeruginosa,* and *Candida albicans* [103]. Using a basally perfused biofilm consortium model consisting of *P. aeruginosa*, MRSA, *Bacteriodes fragilis,* and *Streptococcus pyogenes*, 10 % PVP-I produced the largest overall reduction in bacterial count compared with 0.5 % polyhexanide and 0.05 % silver acetate [106]. However, none of the antiseptics tested eradicated *P. aeruginosa* or MRSA from the biofilms [106]. A further *in vitro* model showed that *Candida auris* biofilms had reduced susceptibility against CHX and hydrogen peroxide, with eradication achieved only using PVP-I [105]. Iodine-containing wound dressings have also demonstrated greater antimicrobial efficacy against mature biofilms of *P. aeruginosa* and *S. aureus* compared with silver-based dressings using an *in vitro* static diffusion model [109].

Rapid onset of PVP-I antibiofilm efficacy has been demonstrated *in vitro*, with complete eradication of mature biofilms of *S. aureus* and *P. aeruginosa* achieved after only 15 min exposure [104]. Conversely,

Schmidt et al. suggested that while PVP-I was effective for *S. epidermidis* eradication *in vitro*, high concentrations or long exposure times may be required for biofilm penetration (10 % for 1 min or 3.5 % for 10 min) [108].

Alves et al. have recently proposed an algorithm for the management of chronic, non-healing wounds due to critical colonization (a specific phase of the infection continuum, characterized by the presence of a bacterial biofilm without overt infection) and/or biofilms to prevent the progression of a wound toward infection [111]. The algorithm includes guidance on mechanical washing of the wound with soap or PVP-I scrub solution, debridement, disinfection with PVP-I dermic solution on gauze, and control of biofilm regrowth using PVP-I gel with or without PVP-I tulle with secondary dressings [111]. Currently, there is no such algorithm or guidelines for biofilm prevention or management during surgery. Given the clinical significance of biofilms in surgery and their role in the development of SSIs, a common protocol for the prevention of biofilms during surgery across all surgical specialties would be beneficial.

PVP-I concentration for intraoperative wound irrigation

The optimal concentration of aqueous PVP-I for intraoperative irrigation is not clear [112]: concentrations used in published literature range from 0.35 %–3.5 % [80,113]. The concentration of PVP-I determines its antimicrobial activity [114]: povidone is hydrophilic and acts as a carrier of iodine to cell membranes. Once the PVP-I complex reaches the cell wall, free iodine is released and is rapidly cytotoxic [115], with a broad spectrum of antimicrobial activity irrespective of the pathogen type (ie, Gram-positive bacteria, Gram-negative bacteria, fungi, viruses, or spores) [8]. The free iodine concentration increases with more dilute concentrations of PVP-I, with a maximal free iodine concentration of 24 ppm at 0.7 % [116]. This paradoxical effect follows a “bell curve”: concentrations <0.05 % lose their PVP-I complex characteristics and behave like aqueous iodine [116]. Thus, the *in vitro* bactericidal efficacy of PVP-I has been shown to increase correspondingly at more dilute concentrations of 0.1 %–1 % [115,117].

Several studies have investigated the activity of different aqueous PVP-I dilutions, including a seminal study comparing the potency of PVP-I and CHX against MRSA [17]. In this study, the bactericidal activity of the two antiseptics was measured using logarithmic reduction factors (LRFs) obtained over a range of exposure times and bacterial strains (33 MRSA isolates). Full antiseptic efficacy was defined as 30 s LRF > 5. PVP-I achieved a significantly higher LRF than CHX, indicating higher microbicidal activity, when averaged over all dilutions, exposure times, and bacterial strains (PVP-I: 4.550–4.879; CHX: 2.735–3.004, depending on the suspension test method used). After 5 min of exposure, CHX did not reach an LRF > 5 at any dilution. The activity of CHX reduced linearly with increasing dilution factor from the minimum dilution factor tested. In contrast, PVP-I had a 5-min LRF > 5 at dilution factors 25–200; PVP-I activity was diminished only at dilution factors higher than 200, thus differing significantly from the linear relationship that was seen with CHX ($P < 0.001$). Compared with CHX, PVP-I had a higher microbicidal activity and remained active at greater dilution factors. Most importantly, PVP-I had the capacity to achieve a 30-s LRF > 5, while CHX did not [17].

In an *in vitro* study, bacteria (*S. aureus* and *S. epidermidis*) and human cells (fibroblasts and mesenchymal stromal cells) were exposed to aqueous solutions of polyhexanide, hydrogen peroxide, octenidine, PVP-I, and CHX at various dilutions for 2 min. Except for polyhexanide, all the antiseptics were bactericidal and cytotoxic at the commercially available concentrations. When diluted, only PVP-I was bactericidal at a concentration that showed remaining cell viability (minimum bactericidal concentration = 1.32 g/L), thus the authors concluded that PVP-I diluted to this concentration could be the optimal antiseptic for intraoperative irrigation [118]; however, clinical studies are required to validate this finding. Prospective clinical studies are required to determine the optimal concentration of PVP-I for intraoperative irrigation and to produce evidence to support a guideline statement on the topic.

iii) Postoperative antisepsis

Postoperative surgical wound management with antiseptics is not included in the WHO or CDC guidelines for SSI prevention [2,5]; however, in contaminated and dirty wounds requiring surgical attention, antisepsis is warranted, combined with systemic antibiotics [9]. Of note, surgical wounds healing by secondary intention (ie, without the use of sutures, staples, adhesives, or clips) have an increased risk of infection that may impact wound healing. Antiseptic or antibiotic agents may be used with the aim of preventing or treating such infections [119]. Antisepsis may also be beneficial for surgical skin graft wounds [9].

Historically, a limited range of antimicrobial products have been available to treat wound infections and reduce bacterial burden [120]. One of them is a dressing containing 10 % PVP-I (INADINE™) [58]. Today, there are several alternative antimicrobial wound products available, including CHX, silver, benzalkonium chloride, triclosan, octenidine, and polyhexanide [9,121].

When using antiseptics for wound healing, their cytotoxic effects must be considered. All antiseptics may have a certain level of cytotoxicity due to nonspecific effects [9]. Given that any cytotoxic effect could potentially affect normal tissue repair [122], selection of a topical antiseptic for wound repair must balance its bactericidal activity and its potential cytotoxicity, in order to create an optimal environment for wound repair [123]. Studies have shown that PVP-I has very low cytotoxicity compared with other antiseptics when tested on skin and oromucosal cell lines [9]. A study of patients with chronic leg ulcers found that application of PVP-I did not alter the microvasculature, nor significantly reduce the density of dendrocytes or fibroblasts; PVP-I was not associated with dendrocytoclasis [124].

Fundamentally, it is also important to confirm that postoperative antisepsis will not impede the wound-healing process. In a clinical trial of patients undergoing split skin grafts, the use of PVP-I ointmentmedicated gauze did not delay wound healing compared with simple Vaseline® petrolatum gauze. Evidence also suggested a possible earlier onset of epithelialization with PVP-I, and a trend toward lower bacterial counts *versus* the petrolatum gauze controls [125]. Interestingly, Eming et al. proposed a novel mechanism for PVP-I action in promoting wound healing: *in vitro*, PVP-I was shown to reduce the activity of plasmin and neutrophil elastase, as well as overall metalloproteinase activity [126]. Metalloproteinases, plasmin, and elastase are all proteases that contribute to perturbation of tissue repair in chronic wounds [126]. Low doses of PVP-I significantly inhibited purified plasmin and neutrophil elastase activity; when tested in wound fluid, there was a dose-dependent inhibition of neutrophil elastase activity by PVP-I. As a strong oxidative agent, iodine can cause denaturation of enzymes by reacting with the amino, phenol, and sulfhydryl groups of their composite amino acids [126]. The resultant loss of enzymatic function may represent PVP-I's mechanism of action. Based on these findings, the authors recommended using PVP-I in impaired wound healing when healing is poorly progressing, strongly exudating, and excessive protease levels predominate [126].

Further evidence for PVP-I's ability to promote healing was provided by investigations in an animal model: the application of 0.5 % PVP-I to acute skin wounds on the dorsal skin of rats for 1 h per day for the first 5 days after injury enhanced healing through upregulation of transforming growth factor beta (TGF-β), which suppressed the inflammatory response and promoted the formation of “more organized” granulation tissue [127]. Here the authors suggested that topical application of PVP-I may be suitable to promote healing, even in the absence of infection [127].

Conclusions

Due to the growing global incidence of antibiotic resistance, greater emphasis should be placed on the use of antiseptics in the prevention of SSIs, given their lower tendency to induce bacterial resistance and

cross-resistance. This review has highlighted the body of evidence supporting the use of PVP-I for SSI prevention at every stage of surgical intervention, from preoperative measures (including skin preparation, preoperative washing, and nasal decolonization) to intraoperative irrigation, through to postoperative wound management. Furthermore, aqueous-based iodine solutions, such as PVP-I, are one of the few antiseptics that can be safely used on mucous membrane surfaces. However, there is a need for more stringent study designs in clinical trials to enable meaningful comparisons between antiseptic agents, particularly for preoperative skin preparation. Until then, the WHO guidelines for surgical site preparation may benefit from a more neutral and balanced position between PVP-I and CHX, recommending the use of alcohol-based antisepsis with either agent. The use of a single agent (PVP-I) for antisepsis throughout each stage of the surgical procedure could be economically beneficial compared with agents that can only be used at discrete stages, and could be advantageous in countries with limited access to other agents.

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CRediT authorship contribution statement

Stan J. Monstrey contributed to conceptualization, project administration, supervision and writing (reviewing and editing). Kris Govaers contributed to conceptualization and writing (reviewing and editing). Patrice Lejuste contributed to conceptualization and writing (reviewing and editing). Didier Lepelletier contributed to conceptualization and writing (reviewing and editing). Paulo Ribeiro de Oliveira contributed to conceptualization and writing (reviewing and editing). All authors have made a direct and substantial contribution to the work reported in this manuscript by participating in each of the following three areas: conceiving and designing the review article; writing the manuscript or providing critical revisions that are important for the intellectual content; and approving the final version of the manuscript.

Declaration of competing interest

SM declares that he has nothing to disclose. DL has served as a consultant for Viatris. KG declares that he has nothing to disclose. PL has served as a consultant for Viatris. PRO declares that he has nothing to disclose.

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