Antiseptics in the era of bacterial resistance: a focus on povidone iodine

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Practice Points

- Increasing bacterial resistance to antibiotics makes the management of superficial skin infections a major medical challenge. Antiseptics have broader spectrums of antimicrobial activity and a reduced potential for selection of bacterial resistance, relative to antibiotics. Consequently, antiseptics are appropriate alternatives to antibiotics for the prevention and treatment of superficial skin infections.
- Of four widely used antiseptics (povidone iodine, polihexanide, chlorhexidine and octenidine), povidone iodine has a particularly broad spectrum of antimicrobial activity that includes Gram-positive and Gram-negative bacteria, bacterial spores, fungi, protozoa and viruses.
- Widespread and extended use of povidone iodine is not associated with the selection of resistant bacterial strains. In contrast, bacterial resistance to chlorhexidine, quaternary ammonium salts, silver and triclosan has been documented.
- Regarding duration of effect on healthy skin, chlorhexidine is active for 1–4 h, whereas solutions of povidone iodine are active for 12–14 h.
- Aqueous and hydroalcoholic formulations of povidone iodine have good skin tolerance. Povidone iodine scrub has better skin tolerance than soap formulations of chlorhexidine and quaternary ammonium compounds (e.g., benzalkonium chloride and cetrimide).
- There is an urgent need for well-designed studies directly comparing the clinical and economic profiles of antiseptics in this setting; nonetheless, povidone iodine can be considered as a first-choice antiseptic in the management of superficial skin infections.

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SUMMARY Antiseptics have broader spectrums of antimicrobial activity than antibiotics and a much lower risk of bacterial resistance selection. Antiseptics are therefore appropriate alternatives to antibiotics for the management of localized superficial skin infections. Povidone iodine has the broadest spectrum of antimicrobial activity of the available antiseptics, and has a rapid and persistent microbicidal effect. It is active against Gram-positive and -negative bacteria, bacterial spores, fungi, protozoa and several viruses, including H1N1 influenza virus (swine flu). It also has good skin tolerance, and is only a weak allergen: it is rarely associated with immediate allergic reactions, which are more prevalent with chlorhexidine. It has also been shown to promote wound healing. Although additional data are needed from well-designed clinical trials, povidone iodine 10% can be considered as a first-choice antiseptic for the prevention and treatment of superficial skin infections.

Resistance to antibiotic treatment is becoming increasingly reported, thus making the management of superficial skin infections a major medical challenge [1]. However, antiseptics (e.g., povidone iodine, polihexanide, chlorhexidine and octenidine; shown in **Figure 1**) are often appropriate alternatives to antimicrobial chemotherapy, and current guidelines advocate the use of wound antiseptics when infections are localized and have not spread systemically [1,101]. Local treatment with antiseptics is expected to become even more prominent in future wound management strategies, since antiseptics have broad spectrums of antimicrobial activity, and are available in convenient and well-tolerated formulations [1]. Indeed, the spectrums of antibacterial activity are broader for antiseptics than antibiotics and, because of several sites of action on bacteria, antiseptics have a much lower risk (or absence) of bacterial resistance selection [2].

Patients with burns are especially susceptible to colonization or contamination of wounds owing to large wound areas and the presence of exudates and necrotic tissue in wound beds. Antiseptic prophylaxis is therefore appropriate. It is also required to prevent secondary wound infection (resulting from surface microbes migrating into deeper tissues) in patients with trauma wounds from bites, stabbing incidents or traffic accidents. Generally, a single application of antiseptic is needed for contaminated intact skin or where wound access and tissue perfusion are good, whereas repeated cleansing with antiseptic until elimination of infection is required for clinically infected wounds [2,101].

The purpose of the current article is to provide an overview of four commonly available antiseptics used in superficial skin infections in the era of increasing bacterial resistance, with a specific focus on the role and place of povidone iodine. Data sources included a bibliographic search using MEDLINE, conference proceedings and company databases from 1980 to 2013. The selected reference list was investigated to identify any key literature not available on MEDLINE and this was augmented by reviews and important articles known to the authors.

Mechanisms of antiseptic action

Antiseptics can be considered in two classes, according to molecular size of the antimicrobial constituent. Small molecules (e.g., diiodine, also referred to as 'free iodine', from povidone iodine) readily penetrate bacterial membrane channels (porins) and cause oxidation of proteins within the bacterial cytoplasm, whereas large molecules (e.g., chlorhexidine) cannot pass through porins and must adsorb to the microbial membrane before activity. Porins are present in the plasma membrane of Gram-positive bacteria, and in both the outer and plasma membranes of Gram-negative bacteria.

In the case of povidone iodine, diiodine is released gradually from a neutral polymer base (polyvinylpyrrolidone), and subsequent microbial membrane penetration of free iodine and intracytoplasmic protein oxidation cannot be stopped. Thus, povidone iodine has a particularly broad spectrum of antimicrobial activity [3] and a lack of chromosome- or plasmid-mediated bacterial resistance. However, povidone iodine has variable activity against Actinobacteria (e.g., *Corynebacterium* spp., *Mycobacterium* spp. and *Nocardia* spp., among others), since these

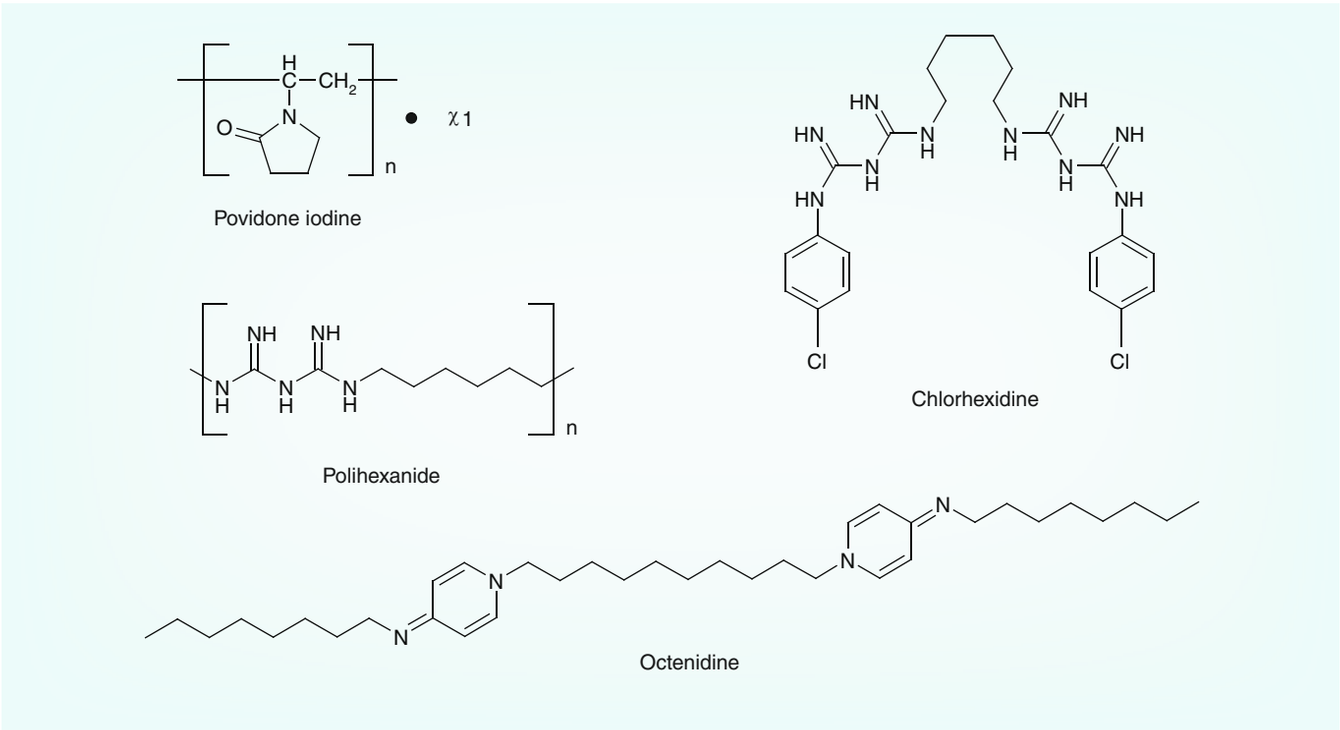

Figure 1. Selected antiseptics.

microorganisms have cell walls with a high mycolic acid content, which makes it difficult for free iodine to penetrate.

The large molecular size of chlorhexidine dictates that the compound cannot pass through microbial membrane porins. As a cationic *bis*-biguanide, it readily adsorbs to negatively charged peptidoglycans in Gram-positive bacterial cell walls, whereas adsorption to the outer membrane of Gram-negative bacteria is less predictable. At low concentrations, chlorhexidine is bacteriostatic, since it causes breakdown of microbial cell membranes [4]. At high concentrations it is bactericidal, as it alters the membrane resulting in its destruction with leakage of cellular contents from cells; it also causes coagulation of cellular contents, with nucleic acid and protein precipitation, contributing to the death of the bacteria.

Overall, lack of adsorption to some Gram-negative bacterial cell membranes explains the 'incomplete' spectrum of chlorhexidine activity; for example, chlorhexidine is inactive against various Enterobacteriaceae (e.g., *Serratia* spp. and *Proteus* spp.), *Pseudomonas aeruginosa*, all *Actinobacteria* spp. and all spores [4].

Octenidine, with two noninteracting cationactive centers separated by a long aliphatic hydrocarbon chain, binds readily on negatively charged surfaces of microbial cell envelopes and eukaryotic cell membranes, disrupting microcellular metabolism [5]. Octenidine is barely absorbed through the skin, mucous membranes or wounds [5].

Polihexanide interacts with acidic, negatively charged phospholipids in the bacterial membrane, which leads to increased fluidity, permeability and loss of integrity, followed by death of the organism [1]. Polihexanide is also transferred to the cytoplasm of cells, resulting in the disruption of bacterial metabolism [1].

Which antiseptic to choose?

In dermatology, antiseptics are used widely as prophylaxis or treatment in operating field disinfection, and acute and chronic wound management. For use in these settings, antiseptics should satisfy several requirements, which differ slightly according to whether healthy or infected skin is being treated **(Table 1)**. No antiseptic will meet all listed requirements, and agents are selected based largely on three main desirable characteristics: a broad spectrum of activity; rapidity of action; and persistence of effect either for operating room disinfection (i.e., healthy skin) or treatment of infected skin.

Table 1. Desirable characteristics for antiseptics (based on a discussion panel).

Characteristic	Operating room disinfection (i.e., healthy skin)	Treatment of infected skin or acute/chronic wounds
Broadest spectrum of antimicrobial activity	+++	+++
Rapid effect	+++	+++
Persistent effect	+++	+++
Limited inactivation by organic compounds	+	++
No selection of bacterial resistance	+	++
Good penetration	++	+
Good skin tolerance	+	+++
No, or only weak, allergenic activity	+	++
No cytotoxicity	+	++

+: Desirable; ++: Markedly desirable; +++: Especially desirable.

Broadest spectrum of antimicrobial activity

When assessing the antimicrobial spectrum of repeated antiseptic applications, exposure times and concentrations of active constituents must be considered. Among antiseptics, halogenated derivatives (e.g., povidone iodine) and alcoholic solutions have the most extensive spectrums of antimicrobial activity **(Table 2)** [6].

Povidone iodine has considerable activity against Gram-positive and Gram-negative organisms, fungi and protozoa, and, with increased exposure times, also against spores and various viruses [101], including numerous strains of influenza virus [7–9]. *In vitro*, in the absence of organic stress, the antimicrobial action of povidone iodine is usually rapid (i.e., within 30 s) [101]. Recently, povidone iodine scrub 4 and 7.5%, when tested at four different exposure times (0.25, 0.5, 2.5 and 5 min), has also demonstrated virucidal activity against porcine influenza H1N1 virus in the presence or absence of interfering proteins (fetal calf serum); thus, at an exposure time of 15 s, povidone iodine scrub 4% reduced viral titer by ≥4.64–4.65 $\log_{10}$; the corresponding decrease in viral titer with povidone iodine scrub 7.5% was ≥4.43–4.64 $\log_{10}$ [Meda Pharma, Data on File]. Moreover, several comparative studies have shown that, irrespective of exposure time or dilution, povidone iodine 10% is considerably more effective than chlorhexidine against methicillin-resistant *Staphylococcus aureus* (MRSA) [10–14]. Also, based on currently available literature, povidone iodine appears to be the only antiseptic with demonstrated activity against dermatophyte fungal infections (e.g., caused by species in the *Microsporum* or *Trichophyton* genera) [15–17] and povidone iodine 4% shampoo used twice weekly reduced the carriage of viable spores in children with scalp dermatophytes [15,18].

Polihexanide is a biguanide with a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, atypical organisms (e.g., *Chlamydia* spp. and *Mycoplasma* spp.), and bacteria that form plaques, biofilms or spores; however, polihexanide is inactive against bacterial spores [1,101]. Polihexanide has shown fungicidal activity against fungi such as *Candida* spp. and *Aspergillus* spp., and *in vitro*, the antiseptic has shown virucidal activity against HIV-1 and herpes simplex virus [1], although polihexanide is generally ineffective against viruses in clinical settings [101]. Altogether, the dual mode of polihexanide action – inhibition of metabolism inside bacterial cells and bacterial membrane disruption after interaction with membrane phospholipids – suggests that future bacterial resistance development to polihexanide is unlikely [1].

Chlorhexidine, which is not a halogenated compound, and combinations of chlorhexidine with quaternary ammonium salts (e.g., benzalkonium chloride and cetrimide), have narrower spectrums of antimicrobial activity than povidone iodine; that is, the activity of chlorhexidine is greater against Gram-positive than Gram-negative organisms (e.g., *P. aeruginosa*, *P. mirabilis* and *S. marcescens*), and the antiseptic has relatively limited activity against fungi and enveloped viruses, and no activity against nonenveloped viruses and bacterial spores [5,19–21]. Bacterial strains with resistance to chlorhexidine, quaternary ammonium salts, silver sulfadiazine

and triclosan have been documented [4,22], and epidemics (e.g., infections caused by *S. marcescens* [23,24] or postinjection *Mycobacterium abscessus* infections [25]) associated with solutions containing chlorhexidine or quaternary ammonium salts have also been reported [23–25].

Octenidine also has a wide-ranging spectrum of antimicrobial activity that encompasses Gram-positive and Gram-negative bacteria, MRSA, plaque-forming organisms such as *Actinomyces* spp. and *Streptococcus* spp., atypical organisms such as *Chlamydia* spp. and *Mycoplasma* spp., fungi, and some enveloped viruses (e.g., hepatitis B virus and herpes simplex virus) [5,101]. However, octenidine is ineffective against protozoa and spores [101].

Various other chemical entities with antiseptic properties demonstrate only limited antimicrobial activity. For example, *in vitro,* hydrogen peroxide has relatively low bactericidal activity against vegetative forms of Gram-positive and Gram-negative bacteria, and its activity is reduced by the presence of blood [26,101]. Silver sulfadiazine is bacteriostatic and fungistatic only, and clinically its overall risk:benefit ratio is now considered rather unfavorable [27,101]. Triclosan possesses only low-to-moderate bactericidal and fungicidal activity. The antiseptic activity of potassium permanganate solution (1:10,000), which is sometimes used to reduce leg ulcer weeping via an astringent effect, has been seriously questioned [28].

Rapid effect

Limited data are available regarding the rapidity of antiseptic action in dermatologic settings. Nonetheless, *in vitro* data show that, against methicillin-sensitive *S. aureus* (MSSA) and MRSA, alcohol solutions are bactericidal after 10 s, and povidone iodine 10% is bactericidal after 15–20 s [13]. Usually (*in vitro* and without organic stress) povidone iodine, similar to octenidine, has antimicrobial activity within 30 s [101]. Polihexanide 0.04% has slower general bactericidal activity (within 1–25 min) than povidone iodine and octenidine [5,101], and chlorhexidine is active against MSSA after 20 s, but takes 20 min for activity against MRSA [14]. After a contact time of 1 min without bioburden, octenidine was more effective against *S. aureus*, *Escherichia coli* and *C. albicans* than povidone iodine, polihexanide, chlorhexidine or triclosan [5].

Persistent effect

In terms of duration of effect on healthy skin, solutions of povidone iodine are active for 12–14 h, whereas chlorhexidine is active for only 1–4 h [29]. Lasting bactericidal activity on the skin surface has been reported for iodophors (e.g., povidone iodine) because free iodine penetrates subepidermal layers and subsequently returns to the skin surface [30]. Alcoholic solutions of povidone iodine and chlorhexidine can further prolong the duration of action for these antiseptics. Both polihexanide and octenidine are adsorbed to microbial cell surfaces and therefore have sustained effects over several hours [1,5]; indeed, as octenidine binds readily to negatively charged surfaces and is not absorbed percutaneously, at least a part of the applied substance remains on the site of application, thus

Table 2. Antimicrobial spectrums of activity for four widely used antiseptics.

Antiseptic	Vegetative bacteria			Spores	Fungi	Viruses
	Gram-positive	*Gram-negative*	*Actinobacteria*			
Halogenated compound						
Povidone iodine 10%	BC +++, LS	BC +++, LS	BC ++	SC ++	FC +++, LS	VC ++, LS
Biguanides						
Polihexanide	BC +++, LS	BC +++, LS	NA	NA	FC ++, IS	VC +, IS
Chlorhexidine	BC +++, LS	BC +++, IS	NA	NA	FC ++, IS	VC +, IS
Cationic surfactant						
Octenidine	BC ++, LS	BC ++, IS	NA	NA	FC ++, IS	VC +, IS
Alcohol						
Ethanol 70%	BC +, LS	BC +, LS	BC +	NA	FC +, LS	VC +

+: Weak; ++: Medium; +++: High.
BC: Bactericidal; FC: Fungicidal; IS: Incomplete spectrum; LS: Large spectrum; NA: No activity; SC: Sporicidal; VC: Virucidal.
Data taken from [1,5,6,14,19–21,101].

exerting a sustained antimicrobial effect [5], which is apparent even against transient infections that reach the skin after initial disinfection [31]. This residual effect of octenidine was shown to decrease skin colonization over time in a prospective, observational study evaluating 62 severely immunocompromised patients with 135 central venous catheters; by 2 weeks post-central venous catheter insertion, most cultures were negative [32]. Overall, to ensure appropriate antisepsis, manufacturers' recommended contact times should always be followed.

■ Limited inactivation by organic compounds

All antiseptics undergo some degree of inactivation by organic compounds such as blood, pus and serous fluids, but the extent of inactivation varies from one antiseptic to another. Povidone iodine, for instance, is inactivated to a lesser degree than chlorhexidine, since the iodophor reacts weakly with proteins [6,10,19,30]. Albumin, blood and mucin have been reported to have no major influence on the microbicidal activity of octenidine, whereas cardiolipin and chondroitin sulfate may reduce or abolish such activity [5]. Similarly, blood and albumin have no major effect on the antimicrobial activity of polihexanide, but this antiseptic is also incompatible with chondroitin sulfate [1].

■ No selection of bacterial resistance

This desirable feature of antisepsis is particularly important in light of the current major public health problems posed by resistant bacteria, especially vancomycin-resistant enterococci and MRSA. Additionally, some topical antimicrobial agents such as gentamicin are bactericidal but are generally avoided as they induce bacterial resistance. Careful selection of antiseptics is therefore required to avoid similar resistance problems to those associated with topical antibiotics [33,34]. A recent study, involving >88,000 cases of impetigo, by the Swedish Infection Control Society [35,36] showed that the increased use of fusidic acid in impetigo has led to an epidemic of fusidic acid-resistant *S. aureus* **(Figure 2)**. A large reduction in the fusidic acid prescriptions has subsequently led to a decrease in resistant strains, confirming the correlation between prescription and the selection of resistance **(Figure 2)**.

Although, based on best clinical evidence, topical antibiotics are generally advocated for the treatment of impetigo, antiseptics represent an alternative management option [37], particularly for recurrent infections [38]. Indeed, Szepetiuk and colleagues demonstrated clinical superiority of povidone iodine gel compared with fusidic acid cream in 40 children with impetigo (390 treated lesions); treatment cure was obtained in 67.5 and 15.0% of sites treated with povidone iodine and fusidic acid, respectively [39]. In this study, discrete-to-moderate stinging sensations were reported in 15.0 and 12.5% of povidone iodine- and fusidic acid-treated impetigo lesions, respectively [39].

Furthermore, to reduce any potential for development of microbial resistance to antiseptics, several strategies can be adopted:

- Use antiseptics with the broadest spectrums of antimicrobial activity;
- Remove organic compounds (blood, pus and serous fluids) by showering before antiseptics are applied [40,41];
- Maintain adequate exposure times and local antiseptic concentrations *in vivo*.

Because of the mode of action of halogenated compounds (see 'Mechanisms of antiseptic action' section), widespread and extended use of povidone iodine is not associated with the selection of resistant bacterial strains [33,42]. Bacterial resistance to polihexanide and octenidine has also not been reported and is not anticipated [1,5]. Conversely, bacterial resistance to chlorhexidine, quaternary ammonium salts, silver and triclosan has been documented [6,12,14,19,43], and chlorhexidine-resistant strains of *P. mirabilis* have been identified in a clinical setting [44]. Thus, acquired resistance – which alters bacterial susceptibility by, for example, altering the outer membranes of Gram-negative bacteria and preventing antiseptic adsorption – appears to be increasing. Indeed, genes conferring resistance to chlorhexidine and quaternary ammonium compounds have been identified in up to 42% of *S. aureus* isolates in Europe and Japan [45,46].

■ Good penetration

Antiseptic penetration into deep layers of the skin optimizes antimicrobial activity against resident flora, and such penetration can be increased by mechanical pressure. Thus, antiseptics should be carefully painted onto healthy skin to maximize antimicrobial activity. When

applied with friction, alcohol has been shown to reduce bacterial counts by 1.9–3.0 $\log_{10}$ colony-forming units, compared with a decrease of only 1.0–1.2 $\log_{10}$ colony-forming units when applied without friction [47]. Overall, alcohol maximizes the skin penetration of active antiseptic constituents (e.g., iodine), and whenever possible, the use of alcohol-containing antiseptics should be recommended in clinical settings.

Good skin tolerance

Aqueous and hydroalcoholic formulations of povidone iodine have good skin tolerance [48,49]. In addition, povidone iodine scrub has better skin tolerance than soap formulations of chlorhexidine and quaternary ammonium compounds. In an *in vitro* 3D human skin model, povidone iodine was considerably less irritating than chlorhexidine and quaternary ammonium compounds [50,51]. Thomas Hunt (University of California, San Francisco, USA), stated that "sceptics who put nothing in wounds but the things they put in their eye will be happy to hear that povidone iodine is now used in newborn eyes to prevent ophthalmia neonatorum (a purulent discharge) and the safety is unquestioned" [52]. Furthermore, to our knowledge, there are no clinical studies that report pain induced by the application of an antiseptic.

Generally, iodophors have better tissue tolerability than octenidine/phenoxyethanol combinations and chlorhexidine-containing formulations [101]. For instance, phenoxyethanol is absorbed across the skin, and then undergoes metabolism to phenoxyacetic acid and urinary excretion. In some countries, therefore, use of octenidine alone, rather than the octenidine/phenoxyethanol combination, is recommended for antisepsis of neonatal skin [5]. Polihexanide is generally well tolerated when applied to the skin [1]. When used as standalone preparations, 70–80% ethanol solutions can cause unpleasant stinging [101].

Interestingly, in a study in 30 young adults, corneoxenometry was used to assess the irritant capacity of povidone iodine 7% (Braunol® solution) and 10% (iso-Betadine®) and chlorhexidine 5% (Hibitane®), solutions on three skin areas: the back, forearm and forehead [51]. Colorimetry and colorimetric indices of mildness indicated that povidone iodine 10% had a significantly lower irritant effect on the skin than chlorhexidine ($p < 0.001$) **(Figure 3)**. The variable effect of the povidone iodine 7% solution was attributed to the presence of iodates (stabilizers) in the formulation [51].

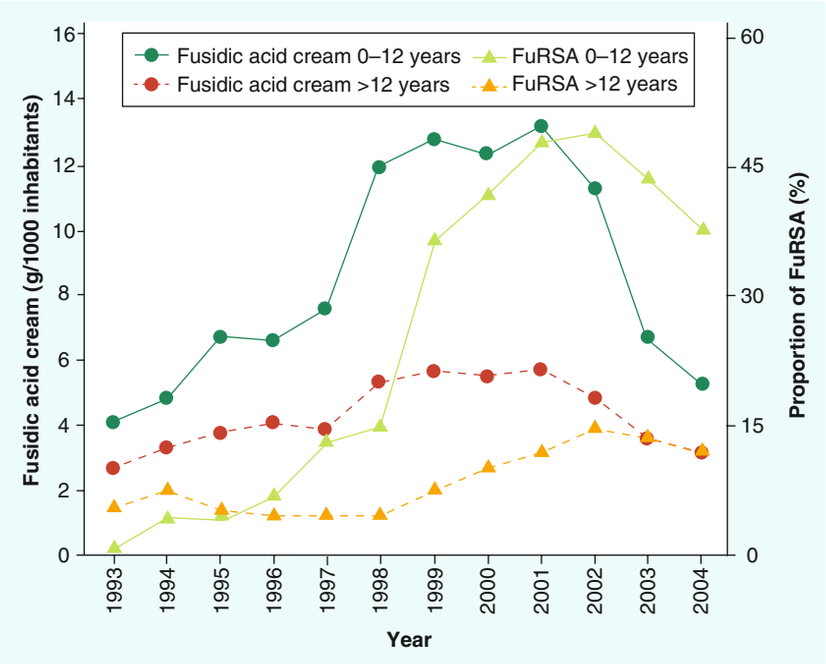

Figure 2. Prevalence of fusidic acid-resistant *Staphylococcus aureus* in Sweden.
Prevalence is shown by age group (0–12 years [solid lines] and >12 years [dashed lines]) and is correlated with the prescription of fusidic acid for impetigo.
FuRSA: Fusidic acid-resistant *Staphylococcus aureus*.
Reproduced with permission from [35].

No, or only weak, allergenic activity

There has been much debate and contention among dermatologists about the potential for allergic contact dermatitis associated with povidone iodine [53–56]. However, it is logical to expect any topically applied antiseptic to have irritant potential, and any major irritation associated with povidone iodine generally results from the use of outdated solutions [54,57]. Furthermore, any definitive diagnosis of allergic contact dermatitis requires a patch test, which is a classical and undebated tool for a proper diagnosis ('gold standard'). Nevertheless, in the specific field of antiseptics, a patch test may generate false positive (irritant) reactions.

Occlusion most probably plays a role in the misinterpretation of patch test results. The Repeated Open Application Test is now universally used when patch test results are considered doubtful. Indeed, by avoiding occlusion (which enhances the irritant effect of antiseptics), it is

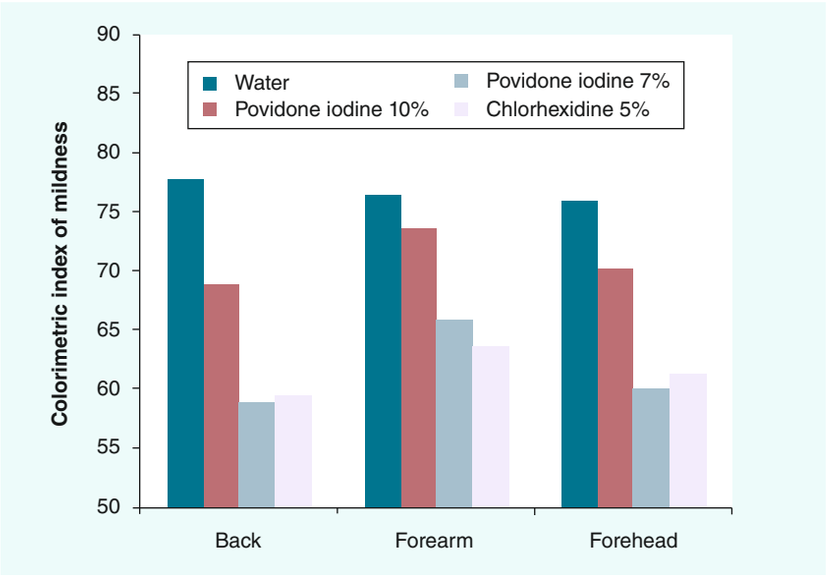

Figure 3. Povidone iodine 10% solution has a significantly lower irritant effect on the skin than chlorhexidine 5% solution ($p < 0.001$). A higher value for colorimetric index of mildness indicates a milder effect on the skin. Data taken from [51].

close to the usual application of antiseptics on the skin, and it is a more precise reflection of reality.

Povidone iodine is considered a weak allergen [58]. In a recent study, 500 consecutive patients were patch tested with povidone iodine 1% [53]. A total of 41 and 39% of patients, respectively, acknowledged applying povidone iodine on the skin/mucous membranes (often repeatedly) or denied/did not recall having used it previously. Patch tests were applied for 2 days (two readings were taken, at 2 and 4 days). At 2 days, 14 (2.8%) patients had a positive patch test to povidone iodine. Tests were still positive after 4 days but with reduced scores. In a second stage (2 weeks later), the 14 positive patients were re-evaluated in a different way. Povidone iodine 10% was applied twice daily (without occlusion) on the volar aspect of the forearm (5 × 5 cm) for 7 days (i.e., repeated open application test). At day 7, only two of the 500 patients were positive (one after four applications, the other after six applications), and the remaining 12 patients (after 14 applications) were negative (false-positives using the patch test). Thus, overall, povidone iodine is considered a weak allergen, with a prevalence of allergenicity of 0.4% [53]. Importantly, there is no relationship between iodine-associated allergic contact dermatitis and anaphylactoid reactions produced by radiologic iodine-contrast compounds (ionic or nonionic); although hypersensitivity reactions to iodinated radiologic contrast media are well documented [59], these reactions are related to the contrast molecule itself rather than to iodine [60].

Povidone iodine is only rarely associated with immediate allergic reactions, which are markedly more prevalent with chlorhexidine [61]. Of 33 patients with a positive chlorhexidine prick test, ten patients had had severe allergic symptoms from chlorhexidine, and 11 had had only mild local symptoms (such as exacerbation of dermatitis). Furthermore, local symptoms from chlorhexidine-containing products may precede more severe attacks [61]. A recent study reported the occurrence of erosive irritant contact dermatitis, an under-recognized complication of chlorhexidine gluconate-impregnated dressings [62]. As young children and immunosuppressed and/or critically ill patients may be more susceptible to the irritant effects of chlorhexidine-containing dressings, healthcare providers need to be aware of this risk and, when chlorhexidine-containing dressings are used, patients should be monitored closely for skin breakdown [62].

While it is not currently possible to directly compare the relative incidence of anaphylaxis after povidone iodine or chlorhexidine, a British drug allergy clinic conducted a 1-year review of anaphylaxis in 23 patients during surgery, reporting one case each of anaphylaxis with povidone iodine (grade two severity) and chlorhexidine (grade three severity) [63].

Octenidine and polihexanide have not been associated with photosensitization or delayed contact sensitization in animal models [1,5]. Relevant data are now needed from human studies to fully define the allergenic potential of octenidine relative to other topically applied antiseptics, but cases of anaphylactoid reactions to polihexanide have been reported. Overall, however, it appears that polihexanide is an uncommon contact allergen, with minimal allergenic potential [1].

■ No cytotoxicity

In vitro data vary widely, but often suggest that certain antiseptics may be cytotoxic [64,65], thus causing some clinicians to consider that repeated use of some antiseptics in chronic wounds may have a detrimental effect on wound healing. However, such *in vitro* findings cannot be generalized to the *in vivo* clinical setting [66]. Thus, in a study in 51 patients with chronic leg ulcers,

povidone iodine significantly increased healing rate (+4 to 18%; $p < 0.01$) and reduced time to healing by 2–9 weeks ($p < 0.01$), whereas chlorhexidine (-1 to +5%) and silver sulfadiazine (+2 to 7%) only modestly improved healing rate [67]. Furthermore, in patients with chronic leg ulcers, povidone iodine 10% did not alter the microvasculature, or significantly reduce the density of dendrocytes, which are required for wound healing, whereas chlorhexidine and silver sulfadiazine did produce such adverse changes [67]. The fact that povidone iodine 10% does not induce the destruction of cells which express coagulation factor XIIIa (which facilitates binding of fibrin to collagen and reshaping of the matrix), supports its lack of clinical cytotoxicity in leg ulcers [67]. In addition, in patients with burns, povidone iodine 10% gel has been shown to increase the rate of wound healing compared with silver sulfadiazine [68].

Some researchers report that the *in vitro* cytotoxic profile of octenidine is similar to that of chlorhexidine and, therefore, markedly worse than that of povidone iodine [5]. Conversely, others stipulate that polihexanide has low *in vitro* cytotoxicity [1], or that the cellular and tissue toxicity of polihexanide is similar to that of the commercially available octenidine/phenoxyethanol combination [101].

Povidone iodine: use in the clinical setting

Numerous commercially produced US FDA-approved preparations of povidone iodine are available. Although 10% povidone iodine remains the standard for presurgical skin disinfection, lower concentrations of povidone iodine (e.g., 1, 4, 5 and 7.5%) are commonly used for a variety of indications and in different formulations (aqueous and alcoholic solutions, scrub, gauzes, ointment and creams). Povidone iodine 10%, for example, is standardized to deliver 1% of biocidal, free molecular iodine [69].

Microbicidal antiseptics (e.g., iodophors, polihexanide and octenidine) are more effective than topically applied microbiostatic antibiotics (e.g., kanamycin, mupirocin, fusidic acid and neomycin), which have several clinical disadvantages **(Box 1)**.

Several clinical studies and/or systematic analyses have demonstrated superior efficacy of chlorhexidine (alcohol-based formulation) compared with povidone iodine (aqueous formulations) for surgical site antisepsis in clean-contaminated surgery [70,71], preoperative surgical site preparation [72], skin preparation for prevention of catheter-related infections [73,74] and skin preparation for blood cultures [75]. However, it is important to note that these comparative outcomes are largely based on data obtained with aqueous povidone iodine and alcohol-based formulations of chlorhexidine. There are currently very few clinical data comparing alcohol-based formulations of povidone iodine and chlorhexidine [76]. A prospective study of three skin preparation protocols concluded that iodophor-based compounds may be superior to chlorhexidine on postoperative wound infection rates [77]. Indeed, a recent systematic review and meta-analysis presented evidence that the perceived efficacy of chlorhexidine in skin antisepsis is often based on the efficacy of alcohol formulations, and that the antiseptic role of alcohol has often been overlooked in evidence assessments [78]. Parienti and colleagues showed that the use of alcoholic povidone iodine for skin disinfection reduced the incidence of catheter colonization and related infection compared with aqueous 10% povidone iodine disinfection in an adult intensive care unit [79]. Furthermore, despite the reported outcomes from clinical studies, there is currently no evidence to suggest that the use of chlorhexidine during hand scrub reduces surgical site infection, which explains why guidelines from WHO, the Centers for Disease Control and Prevention and the Association for Perioperative Practice do not recommend one specific antimicrobial over another for hand scrub [71]. Indeed, current Centers for Disease Control and Prevention guidelines state that, due to the absence of studies comparing alcohol formulations of povidone iodine and chlorhexidine to prepare clear skin, the situation represents an 'unresolved issue' [102], and a 2013 Cochrane

Box 1. Clinical disadvantages of topical antibiotics relative to antiseptics.

- Narrower spectrum of antimicrobial activity
- Microbiostatic rather than microbicidal
- High risk of resistance and crossresistance
- Limited or no activity against multiresistant organisms (e.g., MRSA)
- No residual effect (e.g., because of local metabolism)
- Low concentrations at target site
- Short- and/or long-term cytotoxicity
- Marked allergenic potential

MRSA: Methicillin-resistant *Staphylococcus aureus*.
Data taken from [101].

review, including 13 studies with 2623 participants, concluded that "more research is required to show whether one antiseptic is better than the others at preventing wound infection after clean surgery" [80].

Importantly, as shown in **Table 3**, povidone iodine 10% possesses several of the desirable antiseptic characteristics such as broadest spectrum of antimicrobial activity, rapidity of action, persistent effect and other related characteristics that are discussed throughout this article, and as such, is a first-choice antiseptic for the prevention and treatment of superficial skin infections [2]. Among the wide range of iodophor formulations, product efficacy can vary markedly, depending on the amount of free iodine or diiodine available [101]. That said, povidone iodine has a better tissue tolerability profile than those of octenidine/phenoxyethanol and chlorhexidine, and it is indicated in several clinical settings **(Box 2)**. From a practical perspective, povidone iodine may cause skin/clothing staining but stains on skin and natural fabrics can be removed with soap and water; sodium thiosulfate may be used to remove stains on synthetic fabrics.

The potential risk of hypothyroidism resulting from iodine exposure after administration of povidone iodine has been well documented [81–85], with studies concluding that, in order to mitigate the possible risk, the routine use of iodine-containing antiseptics in very-low-birth weight infants should be avoided [81–83]. In the more recent prospective, controlled study by Brown and coworkers, routine skin-cleansing with povidone iodine was shown not to be commonly associated with transient neonatal hypothyroidism in North America, possibly reflecting differential sensitivity due to prior iodine status [84]. Another study, conducted by Rooman and colleagues, showed that there was no difference in thyroid function between neonates treated with povidone iodine for procedures such as the insertion of catheters or chlorhexidine [85]. Nevertheless, due to potential issues relating to thyroid function with iodine-containing agents, povidone iodine is contraindicated in infants aged <1 month, patients with hyperthyroidism, iodine hypersensitivity or in patients receiving radio-iodine therapy [101]. Povidone iodine is an antiseptic of choice for the topical treatment of infected wounds or acute trauma wounds with colonization. It is also an appropriate antiseptic for pre- and post-operative prophylaxis, and the combination of 39% w/w each of ethanol and 2-propanol with povidone iodine is the first-choice antiseptic for lacerations or stab wounds in HIV-infected individuals or patients with hepatitis B or C virus [101].

In summary, although additional data are needed from well-designed clinical trials directly comparing the clinical utility of antiseptics, povidone iodine 10% can be considered as a first-choice antiseptic for the prevention and treatment of superficial skin infections.

Conclusion & future perspective

In the current era of mounting bacterial resistance to antibiotics, and considering that such resistance can be particularly serious (e.g., in the cases of vancomycin-resistant enterococci and MRSA) interest has been rekindled in antiseptic use for the prevention and treatment of superficial skin infections. Thus, an antiseptic such as the iodophor povidone iodine has several desirable pharmacodynamic properties and clinical characteristics (including no selection of bacterial resistance) that make it an appropriate first-line choice for the management of infected wounds and dermatoses, and for pre- and post-operative prophylaxis. Of major note, povidone iodine 10% has the broadest spectrum of antimicrobial activity of currently available antiseptics, and included in this spectrum are bacterial spores, fungi and

Table 3. Characteristics of current antiseptics in operating room disinfection (i.e., healthy skin) and in the treatment of infected skin.

Characteristic	Antiseptic					Ref.
	Povidone iodine 10%	*Polihexanide*	*Chlorhexidine 2%*	*Octenidine*	*Ethanol 70%*	
Broad spectrum of antimicrobial activity	+++	++	++	++	++	[1,4–22,101]
Rapidity of action	+++	+	++[†]	+++	+++	[5,14,101]
Persistent effect	++	+++	+	+++	+	[1,5,14,29]

+: Least effective; ++: Moderately effective; +++: Most effective.
[†]Active against methicillin-sensitive *Staphylococcus aureus* after 20 s, but takes 20 min for activity against methicillin-resistant *S. aureus* [14].

viruses such as bird flu and H1N1 swine flu. Therefore, this iodophor also has an important clinical role as a hand disinfectant in infection control strategies.

In addition to the treatment of superficial skin infections, there are various uses of antiseptics in the medical field, including hand rub (disinfectant), hand scrub (in the operating room), surgical swab, preoperative body wash and prior to invasive procedures. The various antiseptics are used differently based upon the specific indication that is being treated. Despite the widespread use of antiseptics, no consensus currently exists about which antiseptic is best for each particular clinical setting, with research into the comparative efficacy of antiseptics often being hampered by small sample sizes, varying techniques of skin prepping used and differing concentrations and formulations (e.g., alcoholic or aqueous) of antiseptic evaluated [3]. Thus, there is an urgent need for well-designed, multicenter studies to be conducted to directly compare the clinical and economic profiles of established and emerging antiseptics [1]. Due to concerns relating to potential chemical interaction, the combination of different antiseptics appears to offer no clinical advantage.

Currently, although there is some evidence of clinical benefit for certain antiseptics over others, antiseptic selection for the management of superficial skin infections is largely empirical and based on the limited data available from appropriately designed and conducted clinical trials [1].

General rates of bacterial resistance to antibiotics are likely to continue to increase and, in the management of superficial skin infections, antiseptics may become even more widely used. This is particularly true if, as expected, comparative data accrue from well-designed studies and economic analyses of antiseptics in specific settings. In this way, clinical advantages of one antiseptic over another (e.g., a broader spectrum of antimicrobial activity, a faster and more persistent effect, and no selection of bacterial resistance) will be more clearly defined. Guidelines for antiseptic use can then be developed and clarified, and antiseptics in general will be accurately positioned relative to each other in the prevention and treatment of superficial skin infections. As other clinical data grow, antiseptics with particular virucidal activity (e.g., povidone iodine against H1N1 swine flu) are likely to see increased use in related settings, such as in general hygiene measures (e.g., body disinfection) employed as part of epidemic and pandemic control.

Box 2. Indications for povidone iodine.

Single procedure application

- Antisepsis of intact skin
- Antisepsis of mucous membranes (e.g., before bladder catheterization, biopsies, injections, punctures or surgery)

Repeated, temporally limited applications

- Antisepsis of wounds (e.g., burns, leg ulcers or pressure ulcers)
- Dermatoses with infection or superinfection
- Body disinfection (e.g., for general hygiene or before surgery)

Data taken from [101].

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