An assessment of the evidence on antiseptics: a consensus paper on their use in wound care

Antiseptics are indicated for wounds with localised infection, but there is little robust evidence to guide selection. This consensus paper explores the clinical and research literature to make recommendations for their use in day-to-day practice

wound antisepsis; povidone iodine; octenidine dihydrochloride; polyhexanide; topical antibiotics

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To date 'evidence-based' recommendations for the use of antiseptics on acute and chronic wounds are based on various levels of knowledge **(okay?)**, including clinical experience. No randomised controlled double-blind clinical studies with recognised parameters and comparative procedures for applying antiseptics have been conducted, although first steps are being taken.[1]

In the light of the generally unsatisfactory data on wound antisepsis, this paper set out to investigate active agents that are considered to:

- Have a reliable broad-spectrum effect
- Have a rapid onset of effect[2,3]
- Be efficacious under organic stress (that is, are active when applied in an organ system as opposed to single cells)[2,3]
- Promote wound healing
- Have adequate cell and tissue tolerance (that is, are not toxic)
- Prevent allergy, anaphylaxis, reabsorption and development of resistance.

Author, could you add a sentence or two on this being a consensus document, how the consensus committee was formed, and how you came to the consensus. Thanks Conclusions are based on evidence gained from both *in vitro* studies and clinical practice.

Indications for use

Accurate indications for the use of antiseptics are vital to avoid inhibition of healing or wound damage.[4] Contamination or colonisation of wounds, unless by methicillin-resistant *Staphylococcus aureus* (MRSA), is relatively common and generally does not affect the healing process.[5] However, patients with burns are particularly at risk from contamination due to the extensive wound surface and the presence of non-vital tissue and exudate in the wound bed.[6]

Wound infection can be classed as primary or secondary. Trauma wounds, particularly bites, traffic injuries and stab wounds, have the potential for primary infection — surface microorganisms can migrate into the deeper tissues — so antiseptic prophylaxis is required. Infection developing in an existing wound is secondary.

Generally, localised infection should be treated with antiseptics, systemic infection requires antibiotics, and life-threatening infections such as streptococci in acute necrotising fasciitis need appropriate interventions **such as?**.

Antiseptics: short-term use

The primary aim is to eliminate microorganisms in the wound by surgical debridement, where appropriate, wound cleansing and coverage.[2,3,7,8]

Contaminated injuries with good wound access and intact tissue perfusion require one just application of wound antiseptic. Clinically infected wounds should be cleansed with an antiseptic until the infection is eliminated.[9]

Povidone-iodine

Povidone-iodine is effective against Gram-positive and Gram-negative bacteria, fungi and protozoa and, with a longer exposure time, spores[10] and a range of viruses.[11-13] Like octenidine (Octinisept, Schülke and Mayr), it has a rapid antimicrobial effect — within 30 seconds without organic stress *in vitro*.[14-20] **(TC to check if is available in the UK)**

Studies have demonstrated the activity and efficacy of povidine-iodine **combined with (correct?)** octenidine/phenoxyethanol **(again, not in BNF. UK equivalent?)**.[20,21] Both iodine and octenidine are effective against vegetative bacteria (bacteria in a passive, unproductive state), although octenidine is ineffective against spores and protozoa.[22-25]

Iodine is better tolerated by tissue than a combination of octenidine/phenoxyethanol or preparations containing chlorhexidine, but less well tolerated than polihexanide and taurolidine **(again, not in BNF. UK equivalent?)**.[26-29] **(But are polihexanide and taurolidine less effective than**

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Box 1. Indications for application of povidone-iodine, as specified in the manufacturer's instructions and instructions for use

Single application

Antisepsis of the intact external skin

Antisepsis of mucus membranes — for example, before surgical interventions, biopsies, injections, punctures and catheterisation of the bladder

Repeated, temporarily limited application

Antiseptic wound management — for example, pressure ulcers, leg ulcers, burns

Infected and superinfected dermatoses

Hygienic and surgical hand disinfection

Box 2. Indications for octenidine in combination with phenoxyethanol according to the manufacturers' instructions for application

For repeated, temporally limited antisepsis of mucous membranes and adjacent skin before diagnostic interventions and surgical procedures in the anal/genital area, in the oral cavity, and for temporally limited supporting therapy of interdigital mycoses, as well as adjuvant antiseptic wound management

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10 Gershenfeld, L. Povidone-iodine as a

iodine etc?)

As an active component, therefore, iodine is the agent of choice for topical management of infected wounds or colonised acute trauma wounds.[13-16,18] It can also be used for rinsing deep wounds and body cavities, such as pleura, in a 1:10 solution.[30-32] It is also suitable for pre- and postoperative antiseptic application and is the first choice for pre-operative use in eye surgery.[17,33-37]

A combination of 39 w/w% each of ethanol **and (okay?)** 2-propanol with povidone-iodine is the first choice of antiseptic in stab wounds or lacerations in patients with HIV, hepatitis B or hepatitis C.[38,39]

Intra-articular 0.5% povidone-iodine was well tolerated in rabbits.[39] This was later confirmed *in vitro* on adult bovine cartilage.[40] Studies have demonstrated that tissue compatibility is significantly improved, with no loss of effectiveness, when povidone-iodine is mixed into a liposomal preparation. *In vitro*, even enhanced cell proliferation was observed.[40]

Indications for the use of povidone-iodine are given in Box 1.

In animal experiments, iodophors do not trigger allergic reactions. In humans, this happens rarely.[22] However, the following are contraindicated:

- Hyperthyroidism
- Dermatitis herpetiformis
- Duhring's disease (a polyaetiological syndrome involving focal infections, malign tumors and allergic processes)
- Iodine hypersensitivity
- Radio-iodine therapy.

Iodine is not advised following skin grafting[1] or peritoneal lavage due to the increased risk of tissue intolerance (povidone-iodine can deposit in the liver, and/or adhesiolysis **[please define briefly]** or a shift in the acid-base balance may occur).[23,41]

Finally, clinicians must remember that, depending on the components and concentration of the active agent in the product, the proportion of freely available iodine can vary, influencing its effect.

Octenidine dihydrochloride

Octenidine dihydrochloride, a surface-active agent, is used either in combination with 2% phenoxyethanol or as the sole active agent (in cosmetics). Its antimicrobial activity extends to Gram-positive and Gram-negative bacteria, fungi and certain viruses, but it is ineffective against spores and protozoa.[42-44]

In contrast to iodophors, the exposure time of a 1:1 dilution of an octenidine/phenoxyethanol-based antiseptic without organic stress varies from 30 seconds to over five minutes,[43] depending on the MRSA strain **(author, was this just used on MRSA strains?)**. Against other vegetative pathogens, the full effect unfolds only after five minutes.[28] There is no evidence of carcinogenic, mutagenic, teratogenic, embryotoxic or fertility-impairing activity.[22]

When applied to wounds there is no observed reabsorption.[22] Like povidone-iodine-based antiseptics, dermal application in experimental animals showed no indication of systemic side-effects or neurotoxic reactions.[44]

Cell and tissue toxicity of the commercially available combination of octenidine and phenoxyethanol (Octenisept, Schülke and Mayr) is similar to that of polihexanide. This contradicts empirical clinical reports of successful antisepsis of abrasions, bites and cuts.[45] Surprisingly, in cell cultures, undiluted octenidine seemed less cytotoxic than a diluted octenidine solution. **reference?** This could explain the discrepancy between current *in vitro* findings — obtained with diluted octenidine solutions — and clinical observations.

Occlusive applications with products containing octenidine or povidone-iodine — for example, in combination with bandages or special dressings — are only to be used if recommended by the manufacturer.

Active agents for long-term use

Here, the objective is to interrupt the vicious circle of colonisation → infection → recolonisation → re-infection → delayed wound healing and to eliminate local or systemic factors that delay healing, with the aim of establishing an optimal wound environment.

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Table 1. Further treatment options for colonised or infected wounds

	Effect per single application/side-effects		
Means/method	**Minutes to hours**	**Hours to 1 day**	**Hours to days**
(1–7 days)			
Silver dressings[89,90]			(depending on the product – different duration of activity)
Special measures for local infection treatment			
VAC therapy with polyurethane foam[91]		(daily change of dressing advised by the manufacturer in case of wound infection)	
VAC therapy with polyurethane foam[91]			(may be combined with lavage)
Fly larvae[70,92-96] (*Lucilia sericata*)			(1-4 days)

Polihexanide

Depending on the pathogen and concentration of the agent, the microbicidal activity of polihexanide is slower than iodophores and octenidine (0.04% *in vitro* within 5–20 minutes). It is not effective against viruses and spores, but is effective against *Acanthamoeba keratitis*.[22,19,46-50] Good tissue compatibility — caused by its activity against acid lipids of **in?** bacterial cell membranes, its minor effect on the neutral lipids of human cell membranes,[51] its clinical effectiveness and its ability to support the formation of granulation tissue — makes polihexanide the first choice for non-healing chronic and/or refractory wounds such as second-degree burns and lavage.[22,29,52-59]

According to current knowledge, it appears that, due to its molecular size, polihexanide is not reabsorbed and therefore remains effective only at the site of application.

Initial experiments by Brunner et al. 2003 (personal communication) suggested that polihexanide is compatible with products such alginates and hydrofibres. Due to tissue compatibility and the absence of irritation, application under semi-occlusive and occlusive dressings is possible.[46]

In Germany and Austria polyhexanide is available as a pharmaceutical raw material for the manufacturing of pharmacy-prepared solutions for wound antisepsis. In Switzerland it is registered as a concentrate and pharmacy-prepared solution. In addition, a wound rinse containing undecylenamide-propyl-betaine **(author, please check this is correct. I couldn't find it on the Internet or in the British National Formularly)** as a surface active substance and polyhexanide (combination preparation) as a 'preservative' is available **in which country?** for wound cleansing, moistening and flushing of germs (Sanalind, Paul Hartmann).

Contraindications for polihexanide preparations include:

- Allergies to the active agent and/or ingredients of the applied product
- Application on the hyaline cartilage, central nervous system, the middle and inner ear and inner eye
- First four months of pregnancy.[22]

Polyhexanide may not be used in combination with anionic tensides **(author, tensides is not in any dictionary, please check it is correct and define what it means)** or other wound cleansing soaps, ointments, oils and enzymes etc.[60]

Taurolidine

The active agent taurolidine **(again, not in BNF. UK equivalent?)** has two specific characteristics.[61-65] Due to the slow formaldehyde release[61] *in vitro*, the necessary bactericidal action (reduction factor over 5lg-steps - **author, please explain briefly what g-steps are**) only unfolds after 6–24 hours.[48] It remains effective in the presence of proteins and blood. **(Author, are these the two characteristics? If so, why are they referenced with refs. 62-65. Please clarify)**

Further active agents and methods

Supplemental treatment is needed for problem patients (Table 1). Biosurgery is significantly superior to conventional treatment procedures and usually well accepted by patients,[66-78] although some have occasionally reported pain during application.[6,71,76]

Larvae aid effective debridement and reduce the number of bacteria by up to 5 lg-steps *in vitro*.[71] Indeed, MRSA wound infections have been successfully treated with larvae,[72,73] and preparations containing their haemolymphatic and alimentary secretions have been shown to stimulate fibrob-

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Table 2. Characteristics of obsolete or dispensable active agents for wound antisepsis

Active	Advantage	Disadvantage	Suitable for wound antisepsis
8-Chinolinol	None	insufficiently effective, mutagenic, neurotoxic, allergenic, in animal studies carcinogenic	Dispensable (of minor importance or not essential)
Chloramin T	None	Insufficiently effective, inactivation by blood, allergenic, cytotoxic	Dispensable
Chlorhexidine	Remnant	Gap in efficacy spectrum, cytotoxic, mutagenic, reversible pre-malignant changes in the mouth of rats, anaphylaxis, neurotoxic, resorption?	Dispensable, not for application in the peritoneal area
Ethanol	10% enhanced wound healing in vitro[4,9]	70% solution causes stinging	10% solution in combination with other antiseptics useful, 70-80 % solution where alternatives unavailable may be used as a stand alone
Ethacridine lactate	None	Allergenic, delays wound healing, in vitro mutagenic, more toxic than modern antiseptics (sc LD50 about 1/20 of PVP-I), insufficiently effective, resistance development, not stabile under the influence of light	Obsolete
Dyes	None	Insufficiently effective, topical sensitisation, possible systemic risks **(authors, correct?)**	Obsolete
Nitrofural	None	Insufficiently effective, mutagenic, allergenic, induced benign tumors, resorption in wounds, resistance development possible	Dispensable
Organic mercury compounds	None	Pathogen-dependent, sometimes ineffective , systemic side effects, sensitizing, environmental impact	Obsolete
Quats	None	Insufficiently effective, cytotoxic, resorptive risks, resistance dNevelopment	Dispensable
SSD (silver sulphadiazine)	Temporarily comfortable, cooling	Insufficient microbicidal activity n vitro, resistance development, cytotoxic, systemic risks, allergenic, formation of disturbing protein-wound exudate complexes (scab)	Dispensable
Hydrogen peroxide 3%	Cleansing intact skin from e.g. blood particles via O2 formation	Insufficiently effective, inactivated by blood, cytotoxic	Dispensable

lasts, which reached 12% of the amount of the stimulation induced by epidermal growth factor (EGF).[78] When compared with hydrogels, the cost of larvae therapy was found to be significantly lower due to accelerated wound closure, lower material costs and the reduced need for antibiotics.[6]

For different reasons, such as effectiveness, tolerance/toxicity, the antiseptics listed in Table 2 are not suitable for general use, or are reserved for special situations **such as?**.[2,3,9,17,19,22,29,79-83]

Silver sulphadiazine

Silver sulphadiazine, a complex of silver and sulphadiazine (a sulphone amide), is used in the treatment of burns before surgical necrotomy. As its benefit:risk ratio is being viewed ever more critically, a more detailed assessment seems appropriate.

It can be assumed that, with the use of microbiostatically active agents such as silver sulphadiazine, an effect can only be expected if the bacterial burden is low (less than 10^5 CFU **(please write in full)**/g tissue).[79] The cytotoxicity[80-84] of this active agent could well be the cause of the delayed epidermal regeneration, which occurs alongside transient signs of a reaction similar to dermatitis, with spongiosis, parakeratosis and pseudocarcinomatosis.[79]

When applied to burn injuries, silver concentrations in the blood of up to 440µg/l and in urine of up to 12µg/l have been measured, which may become toxicologically and **allergologically (author, is this a proper word?)** relevant.[83] It is advisable, therefore, to monitor silver absorption in ▶

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blood and/or urine.

In patients with sulphone amide hypersensitivity and renal insufficiency, the use of silver sulphadiazine is strictly contraindicated and the possibility of developing resistance to silver ions, a cross-resistance to systemically administered sulphonamides, should be considered.[84]

Applying silver nitrate to chronic wounds before skin grafting has induced deep necrosis and surface oedema of the corium and/or fatty tissue, as well as fibrin deposits. **reference 85?** In superficial fibrin, minor infiltration by cylindrical cells and granulocytes was observed **reference 85?**. In the deep vessels endothelial cells swelled, and there was leucostasis and a leucocytoclastic penetration of the vessel walls, which could be an expression of a toxic substance reaction. The skin layer directly on the surface consisted of virtually only a necrotic zone with granulocyte infiltration.[85]

Obsolete or dispensable active agents

This includes all substances and combinations of substances that — due to their uncertain effectiveness, critical cytotoxicity, irritation and allergy potential, pain induction, development of resistance and/or absorptive risks — are not or are no longer recommendable for application, or for which proof of efficacy is lacking.

Wounds requiring immediate surgical intervention, such as necrotising fasciitis and deep dermal burns, should not be given antiseptics as a first-line treatment. Necrotising fasciitis is a rare, rapidly progressive, soft-tissue infection characterised by extensive necrosis of the skin and subcutaneous tissue. For both wound types, use of an antiseptic may be considered after surgical intervention.[86]

Topical antibiotics

These products, which include neomycin, kanamycin **(again, TC to check in BNF. UK equivalent?)** and mupirocin, can only be applied topically due to their lack of absorption and/or systemic toxicity. However, their use is opposed because of their:

- Narrow spectrum of effectivity
- Inadequate — essentially only microbiostatic — efficacy[87]
- Potential for resistance and cross-resistance
- Insufficient or no activity against multiresistant pathogens such as MRSA
- Lack of remnant efficacy — for example, due to local metabolism
- Insufficient concentration at the site where the effect is required
- Cytotoxic potential in long-term use, often already in short-term use[41]
- Pronounced allergy potential.[88]

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Antimicrobial chemotherapeutics

When treating infected wounds, as in prophylaxis, clinicians must determine whether the infection can be controlled with topical agents or if adjuvant systemic antimicrobial agents are necessary. The following should be considered:

- Antiseptics with a microbicidal effect such as iodophors, octenidine, polyhexanide are more effective than microbiostatic topical antibiotics. For example, a number of antibiotics have failed to decontaminate nasal MRSA,[87] whereas iodophors have suceeded.[52]
- Used and selected correctly, antiseptics are less cytotoxic than antibiotics[41]
- Topical application ensures an antiseptically effective concentration in tissue without producing an antimicrobially effective concentration in the rest of organism, thereby reducing the risk of systemic side-effects

Conclusion

In contrast to antibiotics, wound antiseptics are available which have no allergenic risks due to the structure of their active agents.

Although the above recommendations will help support decision-making, they do not represent all of the scientific data relevant for deciding which antiseptic product is indicated for which type of wound.

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