

CONSENSUS PAPER ON WOUND ANTISEPSIS

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Summary

Based on both a critical analysis of the current literature and clinical experience, the active agents currently used for antiseptic prophylaxis and the treatment of wound infections are comparatively evaluated. In acutely infected or colonised wounds, PVP-iodine and octenidine-based antiseptics are principally of equal value. For chronic poorly-healing wounds, polyhexanide was shown to be the first choice. Agents unsuitable for wound antiseptics are mentioned to provide orientation.

Introduction

Evidence-based recommendations on the use of antiseptics for the treatment of acute and chronic wounds by experts of different disciplines and countries are given on the basis of what is currently known, including clinical experience. Currently, no randomised controlled double-blind clinical studies with generally recognised parameters and comparative procedures for applying antiseptics have been conducted, which is a limitation. The availability of such studies would make an evaluation possible beyond the recommendations presented here.

Given the generally unsatisfactory data in the field of wound antiseptics, we have explored active agents considered to;

- Have a reliable broad-spectrum effect
- Have a rapid onset of effect ^{2,3} (Kramer et al 93, Kramer et al 95)
- Have efficacy under organic stress
- Promote wound healing
- Have adequate cell and tissue tolerance
- Have an absence of allergenicity, anaphylaxis, reabsorptive risks, development of resistance.

Conclusions are based both on the effects of in vitro studies and on clinical practice.

Indications for use

Accurate indications for use of antiseptic are essential to avoid inhibition of healing⁴. (Kramer 99) Minor contamination or colonisation of wounds is common, and generally does not affect the healing process⁵ (erneut verändert zu unserer Version) Entscheidung AK. (Zastrow & Kramer 01) with the exception for example, colonisation by Methicillin Resistant Staph.aureus (MRSA), which should be treated. Although wounds caused by thermal trauma are primarily almost bacteria free, non-viable tissue and exudates in the wound bed form an ideal environment for bacteria and fungi to proliferate⁶. (Tompkins & Burke 92)

Contaminated trauma wounds, and those showing signs and symptoms of a clinically manifest infection require antiseptic treatment because;

- contaminated trauma wounds have the potential to develop infection
- infection causes a delay in, or failure to heal
- infection, particularly multi-resistant pathogens such as MRSA *may* spread causing sepsis

A distinction is made between primary and secondary infection. Trauma wounds, especially bites, traffic injuries, and stab wounds are primarily infected and surface microorganisms

can extend into the deeper tissues creating a high infection risk. Localised infection should be treated with antiseptics, but wounds demonstrating signs of systemic infection and sepsis require systemic antibiotics in combination with antiseptics. Life-threatening infections such as Streptococci require high doses of systemic antibiotics and topical antiseptics Suitable active agents for wound antiseptics

Short-term use

In cases of contamination, colonisation or infection, the aim is to eliminate microorganisms in the wound. Criteria for antimicrobial selection include its efficacy and sufficient sufficient objective and subjective tissue tolerance without side effects^{2,3} (Kramer et al 93, Kramer et al 95) Principle treatment for infected wounds is surgical debridement of necrotic tissue, wound cleansing and appropriate dressing^{2,3,7,8} (Kramer et al 93, Kramer et al 95, baharestani 99, drager & winter 99).

Contaminated injuries with good wound access and intact tissue perfusion normally require only one application of wound antiseptic. A clinically infected wound requires cleansing with an antiseptic until infection is eliminated, which in general, should take no longer than 2-6 days⁹. (Kramer et al 99)

Povidone iodine

Povidone iodine (PVP) is effective against Gram-positive and Gram-negative bacteria, fungi and protozoa and with a longer exposure time, against spores¹⁰ (gershenfeld 62) and a range of viruses¹¹⁻¹³. (esanau et al 87, wutzler et al 00, daroczy 02) It has a rapid anti-microbial effect (in vitro within 30 seconds without organic stress), which is the same for octenidine¹⁴⁻²⁰. (Octinisept, Schülke & Mayr) (gortz et al 96, michel et al 96, Kramer et al 00, Kramer & b-b 97, mlangeni & daschner 95, Werner 92, pitten et al 03) The effects persist as long as the brown discolouration is seen. Studies have demonstrated the activity and efficacy of PVP iodine and combinations of octenidine/phenoxyethanol at a dilution of 1:20 and an exposure time of an hour.^{20,21}. (pitten et al 03, muller & Kramer 03).

The effects of iodine and octenidine against vegetative bacteria are similar, although octenidine is ineffective against spores and protozoa^{14,22,23} (goertz 96, kramer 01, hierholzer & gortz 84). In vitro, anti-inflammatory effects were demonstrated along with;

- inhibition of expression of bacterial exotoxins and toxin activity
- inhibition of overriding mediator release from human immune effector cells
- decreased influx of activated effector cells
- inactivation of tissue damaging enzymes^{24,25} (konig et al 97, konig et al 97)

Iodine is better tolerated by tissue than a combination of octenidine/phenoxyethanol or preparations that contain chlorhexidine, but less well-tolerated than polihexanide and

taurolidine²⁶⁻²⁹. (Kramer et al 93, Kramer & Adrian 96, Kramer et al 95, Kramer et al 98) As an active component, iodine thus is the agent of choice for topical management of infected wounds or colonised acute trauma wounds^{13-14,18}. (daroczy 02, gortz et al 96, mlangeni & daschner 95) Iodine may also be used for rinsing deep wounds and body cavities (e.g. pleura), using a 1:10 solution³⁰⁻³². (neef et al 96, stobernack & achatzy 96, ETRS 97) . It is not advised following skin grafting due to the risk of failure³², (ETRS 97) or for peritoneal lavage due to an enhanced risk for tissue intolerance (deposit of PVP in the liver, adhesiolysis, shift in the acid-base balance)^{23,33}. (hierholzer & gortz 84, gortz 91) However, iodine may be used for pre- and postoperative antiseptic application. In eye surgery, it is at present the first choice for pre-operative use^{17,34-38}. (Kramer & b-b 97, konig et al 97, b-b & Kramer 02, hara et al 97, binder et al 89, binder et al 99)

After the first phase of induced bleeding, a combination of 39 w/w% each of ethanol/2-propanol with povidone iodine is the first choice of antiseptic in stab wounds or lacerations with HIV, hepatitis B or hepatitis C³⁸. (AWMF 99) In rabbits, intra-articular 0.5% povidone iodine is well tolerated³⁹, (ganzer et al 01) confirmed by in-vitro findings⁴⁰ (Kramer et al 02) on adult bovine cartilage.

Studies have demonstrated that tissue compatibility was significantly improved with no loss of effectiveness when povidone iodine was mixed into a liposomal preparation. In vitro, enhanced cell proliferation was even observed^{1,40,41}. (reimer et al 00, Kramer et al 02, gortz 91)

In animal experiments, iodophors do not trigger allergic reactions, and in humans, only rarely²². (Kramer 01) However, the following are contraindicated:

- hyperthyroidism
- dermatitis herpetiformis During
- iodine hypersensitivity
- application before and after radio-iodine therapy

BOX 1 Indications for the application of povidone iodine solution according to manufacturers' information and instructions for use:

For single application:

- antiseptics of the intact external skin
- antiseptics of mucus membranes such as before surgical interventions, biopsies, injections, punctures, blood sampling and catheterization of the bladder

For repeated, temporally limited application

- antiseptic wound management (e.g., pressure ulcers, leg ulcers, burns),
- infected and superinfected dermatoses
- hygienic and surgical hand disinfection

Clinicians must remember that that depending on the components and the active agent concentration in the product, the proportion of freely available iodine can vary, thus influencing the effect within its area of application.

Octenidine dihydrochloride

Octenidine dihydrochloride, a surface-active agent, is used either in combination with 2% phenoxyethanol or as the sole active agent (in cosmetics). The antimicrobial activity extends to Gram-positive and Gram-negative bacteria, fungi and certain viruses, but it is ineffective against spores and protozoa^{22,44}. (Kramer 01, Kramer et al 03)

Manufacturers guidelines should be followed when using dilutions to ensure effectiveness and prevent side effects⁸ (dragger et al). In contrast to iodophors, the exposure time of a 1:1 dilution of an octenidine/phenoxyethanol-based antiseptic without organic stress varies between 30 seconds and >5 minutes⁴³, (harke 97) depending on MRSA strain. Against other vegetative pathogens, the full effect unfolds only after 5 minutes⁴³. (harke 97) There is no evidence of carcinogenic, mutagenic, teratogenic, embryotoxic or fertility-impairing activity²². (Kramer 01)

When applied to wounds there is no observed reabsorption²². (Kramer 01) Analogous to a PVP-iodine-based antiseptic, dermal application in experimental animals showed no indication of systemic side effects or neurotoxic reactions⁴⁴. (kramer et al 03)

Cell and tissue toxicity of the commercially available combination of octenidine and phenoxyethanol (Octenisept Schülke & Mayr) is similar to that of chlorhexidine²⁹. (Kramer et al 98) but higher than that of iodophors or polihexanide. This contradicts empirical clinical reports of successful antiseptics of abrasions, bites and cuts⁴⁵. (schulke & mayr 97) although

may be explained by unpublished in vitro results, which demonstrated a special interaction between octenidine and matrix components (muller et al in press) To verify these results, further double-blind randomized studies are necessary

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

For repeated, temporally limited antiseptics 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.

Contraindications

Irrigation of peritoneal cavity or bladder, application to the ear drum, patient hypersensitivity to the active agents.

Occlusive applications with products containing octenidine or povidone iodine, e.g., in combination with bandages or special dressings, are only to be used upon recommendation (with medical opinion) of the manufacturer.

Active agents for repeated application in chronic non-healing or sensitive wounds (long-term use)

The objective is to interrupt the vicious circle of 'colonisation – infection – recolonisation – re-infection – delayed wound healing' and eliminate local or systemic factors that delay healing to establish an optimal wound environment

Polihexanide

The microbicidal activity of polihexanide – depending on the pathogen and concentration of the agent – is slower in comparison to iodophores and octenidine (0.04% in vitro within 5-20 minutes). It is not effective against viruses and spores, but effective for *Acanthamoeba keratitis*^{19,22,47-49}. (Werner 92, Kramer 01, bruck et al 00, skripitz & werner 94, Kramer & Rudolph 02, berg 00) Good tissue compatibility, due to its activity against acid lipids of bacterial cell membranes and minor effect on the neutral lipids of human cell membranes,⁵⁰ (ikeda et al 83) and promotion of wound healing (Kramer et al 04 ref 97) combined with its clinical effectiveness, makes polihexanide the first choice for non-healing chronic and/or refractory wounds (e.g., second degree burns), and lavage^{22,29,50-59}. (Kramer 01, Kramer et al 98, ikeda et al 83, berg 00, kallenberger et al 91, Kramer et al 01, sellmer 01, roth et al 85, willengger 95, willengger 94, schmit-neuerburg et al 01)

No statement can be made as yet on the reabsorption of the active ingredient polyhexanide, in long-term application since the sensitivity of existing analytical methods is not sufficient.)

Initial experiments by Brunner et al. 2003 (brunner et al personal communication) have provided evidence of the compatibility of polyhexanide with products such as alginates and hydrofibres used in wound healing. Due to tissue compatibility and the absence of irritation, application under semi-occlusive and occlusive dressings is possible⁴⁷. (bruck et al 00)

In Germany and Austria, polyhexanide is available as a pharmaceutical raw material for the manufacturing of pharmacy-prepared solutions for wound antiseptics. In Switzerland, it is registered as a concentrate and as a pharmacy-prepared solution. In addition, a wound rinse containing undecylenamide-propyl-betaine as a surface active substance and polyhexanide (combination preparation) as a "preservative" is available for wound cleansing, moistening and flushing of germs. (Sanalind Paul Hartmann)

The contraindications for polyhexanide preparations include:

- allergies to the active agent and/or ingredients of the applied product
- application on hyaline cartilage, central nervous system, the middle and inner ear, inner eye
- during the first four months of pregnancy²². (kramer 01)

Polyhexanide may not be used in combination with anionic tensides or other wound cleansing soaps, ointments, oils, enzymes etc⁶⁰. (weuffen et al 84)

Taurolidine

The active agent taurolidine has two specific characteristics. Due to the slow formaldehyde release⁶¹ (reding & pfirman 95) in vitro, the necessary bactericidal action (reduction factor > 5 lg-steps) only unfolds after a period of 6 to 24 hours⁴⁸. (skirpitz & Werner 94) It remains effective in the presence of proteins and blood.

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 patients⁶⁶⁻⁷⁰ (Fleischmann et al 99, wollina et al 02, Sherman et al 02, Sherman et al 03, shermann et al 95) with some patients occasionally reporting pain during application⁶⁷. (wollina et al 02) When compared directly with hydrogels, the cost of maggot therapy was significantly lower due to accelerated wound closure, lower material costs, and reduced use of antibiotics^{71,72}. (wayman et al 00, courtenay et al 00) Maggots aid effective debridement and reduce the

number of bacteria by up to 5 lg-steps in vitro⁷¹. (daeschlein et al 03) Indeed, MRSA wound infections were successfully treated with maggots⁷⁴⁻⁷⁹ (pavillard et al 57, dissemond et al 02, bonn 00, grassberger 02, gallenkemper 99, Thomas et al 99) and preparations of their haemolymphatic and alimentary secretions have been shown to stimulate fibroblasts, which reached 12% of the amount of the stimulation induced by epidermal growth factor (EGF)⁸⁰. (prete 97)

OBSOLETE AND DISPENSABLE ACTIVE AGENTS

This includes all substances and combinations of substances that, due to uncertain effectiveness, critical cytotoxicity, irritation, allergy potential, pain induction, and resistance development.

TOPICAL ANTIBIOTICS

These products e.g., neomycin, kanamycin, mupirocin can only be applied topically due to a lack of absorption and/or their systemic toxicity. However, their use is opposed because of their

narrow effectivity spectrum

inadequate – essentially only microbiostatic – efficacy⁸⁷. (hingst & vergetis 93)

- high risk of developing microbial resistance and cross-resistance
- insufficient or no activity against multi-resistant pathogens (e.g., MRSA)
- lack of remanent efficacy (e.g., 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 use⁴¹ (Kramer et al 02)
- pronounced allergy potential⁸⁸. (kimura & kawada 98)

ANTIMICROBIAL CHEMO-THERAPEUTICS

Topical application of systemic anti-microbial agents is primarily contraindicated due to the risk of developing resistance⁸³. (lyon et al 87) Each case must be assessed to determine whether the infection can be controlled with topical agents, or whether adjuvant systemic antimicrobial agents are necessary. Antiseptics are preferable because; they are more effective than microbiostatic topical antibiotics, they have an effective microbicidal effect without developing bacterial resistance, correctly selected, antiseptics are less cytotoxic than antibiotics⁴⁰. (Kramer et al 02)

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

ANTISEPTICS

For different reasons (effectiveness, tolerance/toxicity), the antiseptics listed in Table 2 should generally not be used, or are reserved for application in special situations^{2,3,9,16,19,22,29,79-83}. (kramer et al 93, kramer et al 95, kramer & b-b 97, Kramer et al 00, Kramer 01, Kramer et al 98, Thomas et al 99, prete 97, hingst & vergetis 93, kimura & kawada, lyon & skurray 87)

Silver sulfadiazine (SSD), a complex of silver and sulfadiazine (a sulfone amide), is used for the treatment of burns prior to surgical necrotomy. Since 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 SSD, an effect can only be expected where the bacterial burden is low (<10⁵ CFU/g tissue) The cytotoxicity⁸⁵⁻⁸⁶ (Zapata-sirvent et al 93, mccauley et al 94,) of this active agent could well be the cause of the delayed epidermal regeneration in connection with transient signs of a reaction similar to dermatitis with spongiosis, parakeratosis and pseudo-carcinomatosis⁸⁴. (hoekstra et al 93)

However, when applied to burns, silver concentrations in the blood of up to 440 µg/l and in urine of up to 12µg/l have been measured, which may become toxicologically and allergologically relevant⁸⁸, (maitre et al 02) so monitoring of silver absorption in blood and/or urine is advised. In patients with sulfone amide hypersensitivity and renal insufficiency, the use of SSD is strictly contraindicated and the possibility of developing resistance to silver ions, a cross-resistance to systemically administered sulfonamides should be considered⁸⁹. (Goodman & gilman 80)

Silver nitrate on chronic wounds before covering with skin grafts has induced deep necroses and surface oedema of the corium and/or fatty tissue, as well as fibrin deposits. In superficial fibrin, minor infiltration by cylindrical cells and granulocytes was observed. The deep vessels showed swelling of endothelial cells, leukostasis, and a leukocytoclastic penetration of the vessel walls, which could be an expression of a toxic substance reaction. The layer which was located directly on the surface consisted practically only of a necrotic zone with granulocyte infiltration^{90,91}. (bruck et al 98, trent et al 98)

CONCLUSION

Based on the current knowledge, it is concluded that although these recommendations offer the basis for supporting decision making, they do not claim to be a complete representation of all scientific data relevant for deciding which antiseptic product is indicated for which type of wound.

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Tab. 1: Further treatment options for colonized or infected wounds

Means / Method	Effect per single application/side effects		
	Minutes to hours	Hours to 1 day	Hours to days (1-7 days)
Silver dressings ⁹²⁻⁹⁵			(depending on the product – different duration of activity)
Special measures for local infection treatment			
VAC therapy with polyurethane foam		(daily change of dressing advised by the manufacturer in case of wound infection)	
VAC therapy with polyurethane foam			(may be combined with lavage)
Fly larvae ^{70,73,74} (<i>Lucilia sericata</i>)			(1-4 days)

Tab. 2: Characteristics of obsolete or dispensable active agents for wound antiseptics

Active	advantage	disadvantage	Suitable for wound antiseptics
8-Chinolol	none	insufficiently effective, mutagenic, neurotoxic, allergenic, in animal studies carcinogenic	dispensable
Chloramin T	broad spectrum of activity, low cytotoxic	allergenic, painful on ulcers	at present benefit risk assessment no definitely possibly
Chlorhexidin ⁹⁶	remanence	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 ⁹⁶	10% enhanced wound healing in vitro	70% solution causes stinging	10% solution in combination with other antiseptics useful, 70-80 % solution in case of unavailable other alternatives (e.g. during travel) may also be used as a stand alone.
Ethacridine lactate	none	Allergenic, delays wound healing, in vitro mutagenic, more toxic than modern antiseptics (sc LD ₅₀ about 1/20 of PVP-I), insufficiently effective, resistance development, not stable under the influence of light	obsolete
dyes	none	Insufficiently effective,	obsolete

		topical sensitization, possible systemic risks	
Nitrofurals	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 development	dispensable
SSD	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 ⁹⁶ 3%	Cleansing intact skin from e.g. blood particles via O ₂ formation	insufficiently effective, inactivated by blood, cytotoxic	dispensable