Clinical study

A practice-oriented recommendation for treatment of critically colonised and locally infected wounds using polihexanide

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- Wound infection;
- Critical colonisation;
- Polihexanide;
- Topical therapy

Abstract
The problem of wound infection presents a special challenge in the treatment of acute as well as chronic wounds. Typical complications not only jeopardise the successful outcome of treatment modalities as a whole; they may result in amputation or even become life-threatening.

Polihexanide is an antimicrobial substance which is highly appropriate for use in critically colonised or infected acute and chronic wounds. This finding is based primarily on the broad antimicrobial spectrum and good cell and tissue compatibility of polihexanide, its capability of binding to organic matrix, the low risk of contact sensitisation, and the fact that it promotes wound healing. Furthermore, there has been no conclusive evidence to date of any pathogens developing resistances under the use of polihexanide.

Summary: Wound infections are special and challenging situations in therapy of acute and chronic wounds. Typical complications are riskful not only for therapeutic process but also for amputation and viability of patients. Polihexanide is an exceedingly appropriate antimicrobial substance for using in critically colonised and local infected acute and chronic wounds. This evaluation is based on different properties of the compound like the broad antimicrobial spectrum, the excellent cell and tissue tolerability, the binding capacity to organic matrix, low risk of contact sensitisation and adjuvant effects to wound healing. Up to now there are no microbial resistances observed.

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Problem at hand

A wound infection is a particularly challenging situation in the treatment of acute as well as chronic wounds. It often involves complications which
jeopardise the successful outcome of the entire therapeutic process; they frequently result in amputation and may even become life-threatening. Polihexanide (polyhexamethylene biguanide, PHMB) is an antiseptic substance which plays a prominent role in wound treatment due to its efficient reduction of microbial loads and excellent tolerability. To date no universal rules have been established for the use of polihexanide. With regard to the efficient use of polihexanide for achieving optimum therapy outcomes, however, there seems to be an urgent need for such rules.

**Objective**

The objective of this study is to devise a therapy recommendation for treatment of critically colonised or locally infected acute and chronic wounds with polihexanide, in an effort to ultimately define a therapy standard. For this purpose, an interdisciplinary expert panel has assembled to gather all currently available evidence on wound antiseptics using polihexanide as an antiseptic agent. The recommendation, addressed to all parties involved either directly or indirectly in the process of wound treatment, is supposed to contribute to a more efficient approach to wound management in daily practice.

**Diagnosis of local wound infection**

The clinical diagnosis of wound infection should be based on the following "traditional" signs of infection:

- redness
- swelling
- hyperthermia
- pain
- limited function

Furthermore, the following parameters should also be considered:

- exudation: substantial increase in the amount of exudates, possibly with increased viscosity, change in colour, fetor ("offensive odour")
- stagnation in the wound healing process, and
- serological signs of systemic infection, e.g. leukocytosis

To date, neither the definition nor the signs of critical colonisation have been universally established [1]. According to a common theory, excessive proliferation of microorganisms may eventually result in a critical microbial load, which in some cases will quickly lead to local infection. More often than not, especially with chronic wounds, critical colonisation is a permanent situation. In this case, the microbial load might trigger an inflammation process, which contributes to a chronification of the wound and involves specific signs such as persistent fibrinous coating (which must by no means be mistaken for pus) [29].

The usefulness and significance of a microbiological diagnosis in the context of wound infection and routine examination of clinically inconspicuous wounds is still a subject of much controversy. A microbiological examination will produce meaningful findings only if there is a clinical infection or, in the case of wounds without any distinct signs of infection, if the condition of the wound is stagnating or actually deteriorating. In these cases, a microbiological examination is indicated; if performed correctly, it may be a factor in therapeutic decision-making.

**Properties of polihexanide**

Polihexanide has a number of special properties and characteristics which make it seem particularly appropriate for use in critically colonised and locally infected acute and chronic wounds. For instance, it is particularly convenient to use.

**Efficacy**

- broad antimicrobial action [3,4,9–11,19,27] (*in vitro*, *in vivo*)
- minimum blood/protein error (reduction of effect on mucous membranes due to presence of mucin) (*in vitro*)
- remanence, post-antiseptic effect (prolonged duration of effect) [26,27] (*in vitro*)
- established promotion of wound healing (depending on concentration) [5–8,20,21] (*in vitro*, *in vivo*)
- additional anti-inflammatory properties [18] (*in vitro*)
- no development of resistances reported to date
- reduction of biofilm [15,16,22] and fibrin [8,17] (*in vitro*)

**Safety**

- good clinical safety [10–14] (*in vivo*)
- specific mechanism of action with regard to acidic lipids of bacterial membranes, with only minor effects on neutral lipids of human cellular membranes [2] (*in vitro*)
Instructions for use

In wound antisepsis, polihexanide solutions are commonly used at concentrations of 0.01%, 0.02%, or 0.04%. The solution should be used only for local applications, e.g., for rinsing (lavage), rinse/suction drainage, or moist wound dressings. As polihexanide has a slow onset of action, and the individual microorganisms respond to the agent with different levels of sensitivity over the course of time, it is important to allow a minimum exposure time of 10–15 min after the wound base has been thoroughly wetted [25]. With regard to appropriate concentration levels of the polihexanide solution, the following information can be used for guidance:

**Therapeutic antisepsis (usually for short-term use)**
- acute, contaminated, severely purulent wounds: use a 0.04% solution
- clinically infected chronic wounds: use a 0.04% solution
- for application in suction/rinse drainage: use a 0.02% solution
- intra-operative wound contamination: use a 0.01% solution for decontamination

**Infection prophylaxis (medium or long-term use as an exception from the rule)**
- (critically colonised) chronic wounds: use a 0.01–0.02% solution, or
- wound dressings containing polihexanide

**Contraindications**
According to current knowledge, polihexanide must not be used [30]
- for peritoneal lavage,
- for antiseptic joint lavage (cartilage toxicity)
- in applications involving any part of the CNS, including the meninges, and intralumbar applications,

**Wound management products containing polihexanide**

Tables 1–6 provide a synopsis of wound management products with polihexanide which are currently available.

**Antiseptic solutions (medicinal products, see Table 1)**. Polihexanide solutions are typically mixed to order by pharmacists, using polihexanide concentrate as a raw material (supplied by various providers). At present, Serasept® (by Serag-Wiesner KG) is the only polihexanide solution available as an approved finished drug product with antiseptic effects.

**Wound rinsing solutions (medical devices, see Table 2)**. The wound rinsing solutions Lavasorb® (Fresenius Kabi GmbH), Lavanid® (Serag-Wiesner KG), and Prontosan® (B.Braun Melsungen AG) are not considered to be antiseptic agents, but medical devices with polihexanide added as a preservative, i.e., they may claim only a purely physical cleansing effect. This also explains the differences in indications and shelf life after first opening stated for solutions of identical composition (cf. Table 1).

Tensides in wound rinsing solutions may reduce the surface tension of the solution, which increases the wettability of the wound surface, and they may further reduce cytotoxicity [3].

**Antiseptic gel preparations (medicinal products mixed to order, see Table 3)**. Indications for medicinal products mixed to order, such as Hydrophilic Polihexanide Gel and Polihexanide/Macrogol Ointment, include the prophylaxis and therapy of infected wounds. The common recommendation for infections with gram-negative pathogens is to use the higher concentration (0.1%) [30]. The relative benefits of the Macrogol ointment as compared to the polihexanide gel include its more solid consistency and high exudate absorption capacity.

**Hydrogels for wound cleansing (medical devices, see Table 4)**. The medical devices Prontosan® wound gel (B. Braun Melsungen AG) and Lavanid® wound gel (Serag-Wiesner KG) claim the “cleansing and moisturising of wounds and preservative moistening of wound dressings” as their intended purpose.

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2 Biocompatibility index (BI): quotient of cell toxicity (IC50) and microbicidal efficacy (RF > lg3 = reduction of microbial counts by more than 3log), tested in FBS (fetal bovine serum). BI is a term first defined in 2006 for better comparability of different antimicrobial substances [31].
**Table 1** Antiseptic solutions (medicinal products).

<table>
<thead>
<tr>
<th>Product</th>
<th>Polihexanide as an active pharmaceutical ingredient (concentration)</th>
<th>Excipients</th>
<th>Manufacturer</th>
<th>Status</th>
<th>Indication (according to manufacturer)</th>
<th>Exposure time (according to manufacturer)</th>
<th>Shelf life after container has been opened (according to manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polihexanide solution, NRF&lt;sup&gt;a&lt;/sup&gt; (Lavasept&lt;sup&gt;b&lt;/sup&gt; solution&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.02%, 0.04% in Ringer’s solution</td>
<td>Macrogol 4000</td>
<td>Pharmacy</td>
<td>Medicinal product mixed to order; no prescription required</td>
<td>Antiseptic solution for prophylaxis and therapy of infected wounds</td>
<td>10–15 min minimum</td>
<td>For single use only; any unused quantities to be discarded after a maximum of 24 h. 7 days with Mini-Spike 28 days with Mini-Spike</td>
</tr>
<tr>
<td>Serasept&lt;sup&gt;b&lt;/sup&gt; solution 1/2</td>
<td>0.02%, 0.04% in Ringer’s solution</td>
<td>Macrogol 4000</td>
<td>Serag-Wiesner KG</td>
<td>Medicinal product; no prescription required</td>
<td>Antiseptic solution for adjuvant treatment of wounds</td>
<td>Not applicable – product is used as a moist wound dressing (impregnated dressing) over a period of 24 h</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Manufacturing instructions, indication, and exposure time according to DAC/NRF ("Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium").

<sup>b</sup> Prepared by use of a 20% polihexanide concentrate (raw material supplied by different providers).
Wound dressings containing polihexanide (medical devices, see Tables 5 and 6). The Covidien products Telfa® A.M.D., Excilon® A.M.D., and Kerlix® A.M.D. are dry wound dressings consisting of cotton impregnated with polihexanide, which is supposed to reduce microbial counts in the dressing. According to Lohmann & Rauscher GmbH & Co KG, their moisture-controlling wound dressing Suprasorb® X + PHMB is to be “used in critically colonised or infected wounds if they are superficial or deep, with low to moderate exudation.”

Used properly and for the purposes intended, polihexanide is a highly effective antiseptic agent; it should be used for periods as long as necessary, but as short as possible. Whenever wound management products with polihexanide are used, the indication must be strictly verified, including the aspect of whether the product is a medical device or a medicinal product with antiseptic effects. Due to the variety of carrier materials for polihexanide, the formulations used to date (wound rinsing solutions, gels, wound dressings) have different properties and characteristics, and thus their intended purposes and clinical effects are also different.

Local (topical) treatment approach with polihexanide and other therapeutic procedures

Starting point of therapy

Acute and chronic wounds may change dramatically within short periods of time, in particular with regard to their microbial situation. In these cases, it is essential for a successful outcome that an adequate therapy be initiated immediately. Beginning from the stage of critical colonisation, a therapy is indicated. “Critical colonisation” is a stage of transition from colonisation (commonly found in wounds healing by second intention) to infection. A specifically targeted local antimicrobial therapy can often prevent this transition to wound infection [1].

The use of antiseptic agents can only be a complement to wound cleansing, but never a substitute for it.

Therapeutic local antisepsis

Once a wound is infected, the following general rule should be followed: local infection should be treated by a local (topical) therapy, and systemic...
Table 3  Gels with polihexanide (medicinal products mixed to order).

<table>
<thead>
<tr>
<th>Product</th>
<th>Polihexanide concentration</th>
<th>Excipients</th>
<th>Manufacturer</th>
<th>Status</th>
<th>Indication</th>
<th>Shelf life after container has been opened (according to manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic polihexanide gel NRF&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.04%, 0.1%</td>
<td>Macrogol 4000, hydroxyethyl cellulose, WFI 95%</td>
<td>Pharmacy</td>
<td>Medicinal product, mixed to order, no prescription required</td>
<td>Prophylaxis and therapy of infected wounds (including cutaneous staphylococci infection in neurodermatitis)</td>
<td>For single use only; any unused quantities to be discarded after a maximum of 24 h</td>
</tr>
<tr>
<td>Polihexanide/ Macrogol ointment NRF&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.04%, 0.1%</td>
<td>Macrogol 400 (tenside), Macrogol 400 (tenside), WFI 10%</td>
<td>Pharmacy</td>
<td>Medicinal product, mixed to order, no prescription required</td>
<td>Superficial wounds which are infected or at risk of infection; as an adjuvant to surgical wound treatment in soft tissue infections</td>
<td>1 year (filled in tubes)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Manufacturing instructions, indication, and exposure time according to DAC/NRF ("Deutscher Arzneimittel-Codex/Neues Rezeptur-Formularium").

<sup>b</sup> Prepared by use of a 20% polihexanide concentrate (raw material supplied by different providers).

<sup>c</sup> Reimbursable as medical practice supplies.
### Table 4  
**Hydrogels used for wound cleansing (medical devices).**

<table>
<thead>
<tr>
<th>Product</th>
<th>Polihexanide concentration</th>
<th>Excipients</th>
<th>Manufacturer</th>
<th>Status</th>
<th>Indication (according to manufacturer)</th>
<th>Shelf life after container has been opened (according to manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavanid® wound gel</td>
<td>0.04%</td>
<td>Macrogol, glycerin, hydroxyethyl cellulose, Ringer’s solution</td>
<td>Serag-Wiesner KG</td>
<td>Medical device of Class IIb</td>
<td>Cleansing and moisturising of wounds; preservative moistening of wound dressings</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Prontosan® wound gel</td>
<td>0.1%</td>
<td>Undecylenamidopropyl betaine (tenside), glycerol, hydroxyethyl cellulose, WFI</td>
<td>B.Braun Melsungen AG</td>
<td>Medical device of Class IIb</td>
<td>Cleansing and moisturising of chronic wounds; preservative moistening of wound dressings</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

### Table 5  
**Wound dressings containing polihexanide (medical devices).**

<table>
<thead>
<tr>
<th>Product</th>
<th>Polihexanide concentration</th>
<th>Dressing material</th>
<th>Manufacturer</th>
<th>Status</th>
<th>Effects (according to manufacturer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telfa® A.M.D. Absorbent dressing; AMD: antimicrobial dressing</td>
<td>0.2%</td>
<td>Absorption pad made of cotton, both sides covered with perforated</td>
<td>Covidien</td>
<td>Medical device of Class IIa</td>
<td>Reduction of microbial counts in the dressing</td>
</tr>
<tr>
<td>Exclion® A.M.D. Split dressing</td>
<td>0.2%</td>
<td>Nonwoven cotton dressing</td>
<td>Covidien</td>
<td>Medical device of Class IIa</td>
<td>Reduction of microbial counts in the dressing</td>
</tr>
<tr>
<td>Kerlix® A.M.D. Dressing/packing gauze/bandage</td>
<td>0.2%</td>
<td>Voluminous cotton gauze product</td>
<td>Covidien</td>
<td>Medical device of Class IIb</td>
<td>Reduction of microbial counts in the dressing</td>
</tr>
</tbody>
</table>
infections by a systemic therapy (the latter may be used in combination with a topical treatment if necessary). The primary reason why the use of antiseptic agents should be preferred in the treatment of local wound infection is the fact that most systemic risks and side effects can be safely ruled out by choosing the appropriate agent; furthermore they are also more economical.

**Duration of treatment/endpoint of antiseptic therapy**

The primary objective of treatment is to eliminate the clinical signs of infection. Local antiseptic treatment usually covers a period of 2–5 days; it should not exceed a maximum of 14–21 days. If the signs of infection fail to improve or resolve, the efficiency of the previous approach should be investigated; if necessary, a new approach should be defined. If the therapy has been successful, treatment should be continued in accordance with the general principles of moist wound management, without the use of any antimicrobial agents.

**Use in prevention therapy**

Polihexanide can also be used for prevention. On this subject, however, only little data has become available to date [28]. From both the therapeutic and the economical perspective, the preventive use of polihexanide always requires a strict indication, which has to be critically evaluated on a regular basis. Any non-specific, unwarranted, or permanent use is unacceptable.

**Use in combination with other therapy modalities**

In any case of contaminated or coated wounds, the use of wound antiseptics such as polihexanide must definitely be complemented by other therapy modalities, e.g. biomechanical debridement. As a matter of course, the original causes of the wound and its development have to be investigated and treated before any therapy is initiated. After that, the general principles of moist wound management should be applied.

**Summary**

Polihexanide is an antimicrobial substance which is highly appropriate for use in critically colonised or infected acute and chronic wounds. This positive assessment is based primarily on the broad use of polihexanide: as an auxiliary pharmaceutical ingredient (medical devices of Class III).
antimicrobial spectrum and good cell and tissue compatibility of polihexanide, its capability of binding to organic matrix, the low risk of contact sensitisation, and the fact that it promotes wound healing. Furthermore, there has been no conclusive evidence to date of any pathogens developing resistances under the use of polihexanide.

The objective of a therapy with polihexanide is to reduce the microbial load of a critically colonised or infected, acute or chronic wound (Fig. 1). Polihexanid must under no circumstances be used as a sole treatment modality. Top priority has to be given to prior surgical debridement and investigation of the causes of the underlying condition, including adequate therapy.

A wide variety of medicinal products and medical devices with polihexanide are available on the market, in various formulations, each with different characteristics and applications. These may be used exclusively in accordance with their respective indications.3

The use of polihexanide for purposes of prophylaxis may also be warranted.

In summary it can be concluded that, based on current scientific knowledge as well as the experience of experts, polihexanide is a tried and proven agent in wound treatment.

**Conflict of interest**

Scientific Grant by Lohmann & Rauscher GmbH & Co KG, Rengsdorf (D).

**References**


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