Wound dressings are intended to protect a wound from mechanical and environmental injuries, microbial contamination, and to promote healing. Selection of a dressing depends on the wound's aetiology, severity, condition, and location. Fundamentally, it is the wound that tells the practitioner which dressing should be selected.

In the past three decades numerous wound dressing types and categories have been developed. Modern wound dressings may be adherent or non-adherent and dressing categories include film, island, methacrylate, moist, absorbent, foam, and super-absorbing. Dressings may be non-antimicrobial or antimicrobial.

Development of infection

An infection occurs following contamination and colonisation by bacteria, when a wound and the surrounding tissue are invaded by pathogens with a subsequent defensive inflammatory reaction. An infection may remain localised or may generalise. The occurrence of wound infection depends on the underlying condition of the patient and associated immune response, the amount of primary contamination and the virulence of the microorganisms involved.

Wound infection may impede the process of healing and eventually lead to severe and life-threatening complications. Promoting healing and protecting a wound from potential contamination, therefore, are both imperative to prevent infection. To this end topical and systemic antibiotics have been widely used in treatment, leading to the consequent bacterial resistance faced today.

During his Nobel Prize lecture on 11 December 1945, Sir Alexander Fleming gave a note of warning: “The time may come when penicillin can be bought by anyone in the shops. Then, there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

Poor antibiotic stewardship has led to the rise of community and healthcare associated infections caused by multi-resistant microorganisms. The research involving new antibiotics and their introduction is not keeping pace with resistance and the need for stewardship has never been greater. At the same time, however, infected wounds are still one of the greatest challenges in medicine.

Antisepsis and dressings

While antibiotic therapy is limited by the induction of antibiotic resistance, today highly effective antiseptic compounds with a broad antimicrobial spectrum are still available, making it foreseeable that local antisepsis will become more important for prevention and treatment of wound infection.

Antisepsis uses antiseptics topically on the wound surface or on surgically exposed tissues. It signifies all antimicrobial measures on or in living tissue and is intended, when indicated prophylactically, to prevent unwanted colonisation or infection.

Antisepsis is achieved primarily by single or repeated topical use of liquid antiseptics, but other modes of application are being used successfully, including the use of antimicrobial wound dressings.

Analysis of 80 different antimicrobial wound dressings available in the central European market revealed that more than 60% (49/80) of antimicrobial wound dressings are based on forms of silver, and 16% (13/80) of antimicrobial wound dressings contain sources of medical honey.

Surprisingly, antimicrobial wound dressings based on other well-established antiseptics such as chlorhexidine digluconate (CHG), Polyhexamethylene biguanide (Polihexanide; PHMB) or povidone-iodine (PVP-I) are less frequently found and account together for less than one fifth (14/80) of all antimicrobial wound dressings available in central Europe. Contrary to these findings, the antiseptics currently recommended for wound antisepsis are Octenidine dihydrochloride (OCT), PHMB, and PVP-I.

While universal agreement on clinical indicators relevant to intervention with antimicrobial dressings remain illusive, it is important to remember that all antimicrobial dressings have different physical and pharmacological properties. These include: their material and the amount of antimicrobial compound they release, the duration and mode of antimicrobial action, the dressing’s ability to manage varying volumes of wound exudate,
or to decrease malodour or pain. The available range of these dressings in clinical practice means that large volumes need to be kept in stock of both antimicrobial and non-antimicrobial dressings.

Selecting antiseptics

Antiseptics carry little risk of resistance as their direct, extremely fast and disruptive action is on multiple, non-specific sites of microbial cell biology. Antiseptics are limited to topical use, however, carrying some risks of toxicity and allergy if use is inadequate or extended.

It is important to note that there are no ‘good’ or ‘bad’ antiseptics, only appropriately or inappropriately used antiseptics.

In recent years, chiefly in Central Europe, the antiseptic concept was systematically explored in-vitro and in clinical practice, predominately in wound care.1 The aim was not to replace antibiotics by antiseptics, but to use antiseptics topically wherever possible, in order to maintain effectiveness of antibiotics for systemic treatment by preventing the development of microbial resistance.

The selection of antiseptic compounds, particularly for prevention or treatment of wound infection, is not trivial.3, 9 Wound antiseptics for use in body cavities or on opened tissues must meet very different requirements with regard to antimicrobial efficacy and tissue tolerability.

Antimicrobial efficacy must be guaranteed even in the protein-rich biotopes of wounds. In the same way, tissue tolerability must be present in order not to interfere with wound healing, and the risk of side effects due to absorption must also be ruled out. A final challenge is to ensure local microbicidal levels with adequate tissue penetration, absent development of resistance, and absent risk of toxic and allergic side effects after local application.

To identify suitability of antimicrobial candidates as wound antiseptics, the biocompatibility index (BCI) was adopted as a standardised in-vitro test.10 This concept allows simultaneous assessment of the antimicrobial efficacy and tissue tolerability.

The BCI is an index of the required concentration to achieve a three log antimicrobial reduction at 30 minutes application time against Staphylococcus aureus and Escherichia coli, respectively, and the cytotoxic concentration of an antiseptic, which kills 50% (IC50) of L929 cells (mouse embryonic fibroblast cells) in-vitro tested under organic challenge using 10% fetal-bovine serum albumin (FBS).

L929 cells react sensitive to cytotoxic stress and therefore are routinely used for in-vitro cytotoxicity assessments. If the index is greater than one, the antiseptic’s antimicrobial efficacy is higher than the corresponding cytotoxicity. If the index is below one, the tested agent is more cytotoxic than antimicrobially active. The BCI of various antiseptics is summarised in Table 1.

Based on the BCI, the current consensus for selection of wound antiseptics in Central Europe recommends OCT, PHMB, and PVP-I as suitable antiseptics for wound antisepsis, since these compounds demonstrate a good

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**Table 1. Bio-compatibility Index of various antiseptics tested after 30 minutes application time against S. aureus or E. coli on L929 cell culture.**

<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>BCI (30 minutes)</th>
<th>L929/E. coli</th>
<th>L929/S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octenidine dihydrochloride (OCT)</td>
<td>1.73</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>Polyhexamethylene bisguanide (PHMB)</td>
<td>1.51</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine digluconate (CHG)</td>
<td>0.83</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Povidone iodine (PVP-I) ointment</td>
<td>0.70</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Povidone iodine (PVP-I) solution</td>
<td>0.68</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Benzalkonium chloride (BAC)</td>
<td>0.63</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Cetylpyridinium chloride (CPC)</td>
<td>0.58</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Triclosan</td>
<td>0.23</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>20% (w/w) silver/protein solution</td>
<td>0.22</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Silver nitrate (AgNO3)</td>
<td>&lt; 0.00</td>
<td>&lt; 0.00</td>
<td></td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>&lt; 0.00</td>
<td>&lt; 0.00</td>
<td></td>
</tr>
</tbody>
</table>

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antimicrobial activity against gram-positive and gram-negative bacteria with low cytotoxicity against fibroblasts.

While PVP-I and CHG are well known outside central Europe, OCT and PHMB have just recently been introduced to the international community. OCT is a cationic antiseptic, which, as a result of the two positive charges in relation to the molecular weight of 437 Daltons, is strongly adsorbed onto negative cell surfaces. OCT reacts with polysaccharides in the cell wall of microorganisms, attacks the enzymatic systems, destroys cell function and leads to leakage of the bacterial or fungal cytoplasmic membrane. As a result, the mitochondrial function is also disturbed.

Furthermore, interaction with salts of the fatty acid glycerol phosphate in bacterial cell membranes serving as main binding partners is discussed. Some findings indicate strong adherence to lipid components in cell membranes (e.g. cardiolipin), which might explain the high antimicrobial activity together with good tolerability for human epithelium and wound tissue.

OCT shows a broad antimicrobial activity against gram-positive and gram-negative bacteria, chlamydiae and fungi. Microbistatic and microbicidal efficacy range is about 10 times higher than that of CHG. A particular feature is the marked residual effect. OCT’s minimal microbicidal concentration of five minutes contact time results in greater than, or equal to, five log reduction for S. aureus, E. coli, Bacillus subtilis and Pseudomonas aeruginosa ranges as result of the two positive charges in relation to the molecular weight of 437 Daltons, is strongly adsorbed onto negative cell surfaces. OCT reacts with polysaccharides in the cell wall of microorganisms, attacks the enzymatic systems, destroys cell function and leads to leakage of the bacterial or fungal cytoplasmic membrane. As a result, the mitochondrial function is also disturbed.

In recent years, preclinical studies and clinical observational trials have confirmed the applicability and suitability of antimicrobial preparations containing OCT. Due to its low cytotoxicity and high antimicrobial efficacy, as seen in Table 1, OCT is a potent candidate for preventing wound infection while not affecting wound healing.

PHMB’s uses range from surface disinfection to antisepsis of skin, mucous membranes and wounds. Due to its unspecific, strong interaction with negatively charged phospholipids, PHMB has a broad antimicrobial spectrum, including gram-positive and gram-negative bacteria, plaque-forming and biofilm-generating bacteria, spore-forming bacteria (but not bacterial spores), intracellular bacteria such as chlamydiae and mycoplasma, and fungi (including Candida spp. as well as Aspergillus spp.).

The minimal microbicidal concentrations of PHMB are: S. aureus: 0.1 µg/ml, Bacillus subtilis: 0.5 µg/ml, Enterococcus faecalis, Streptococcus lactis, E. coli and Enterobacter cloacae: 5 µg/ml, P. aeruginosa and Saccharomyces cerevisiae: 25 µg/ml. In 10% fetal bovine serum, PHMB achieves a three log reduction of S. aureus at a concentration of 100 µg/ml and E. coli in at 90 µg/ml after 30 min contact time, respectively. The in-vitro efficacy corresponds with clinical data and reports.

The most interesting feature of PHMB is its relation between antimicrobial efficacy, low cytotoxicity and exceptional tissue compatibility (Table 1) that has been repeatedly described by independent researchers’ in vitro and in animal models, as well as in controlled clinical studies and case reports.

While the BCI is a good indicator for selection of antiseptic solutions, it does not allow for assessing the suitability of antimicrobial wound dressings. This is a problem for antimicrobial wound dressings, in particular those containing silver and honey.

In order to close this gap, different in-vitro test models have been developed. A recent evaluation of five commercially available silver based antimicrobial dressings on the basis of hydrocolloids, foams or non-woven fabrics used a modification of the BCI concept. Antimicrobial dressings were tested for characteristics of Ag⁺ release, antibacterial activity against S. aureus and P. aeruginosa, and cytotoxicity against V79 cells.
On a first glance, the results (Table 2) seem to confirm a trend that the higher the Ag+-release, the higher the cytotoxicity of the respective silver based dressing. The details of the results, however, showed that cytotoxicity was not simply correlated with the individual dressing’s Ag+-release, but was influenced by water solubility and substrate properties. This study also reconfirmed the variable antimicrobial activity of silver based dressings against gram-positive and gram-negative bacteria. The authors well concluded that the different efficacy and cytotoxicity of the Ag+-dressings should be considered by clinicians during wound management.

Future developments

A recently reintroduced methacrylate dressing has been investigated for its ability to release various antiseptic compounds from its matrix. The dressing, which comes as a powder and transforms into a wound contour conforming matrix once in contact to wound exudate, is based on dehydrated hydrogel modified into nanoparticles containing an 85:15 blend of poly-2-hydroxyethyl-/poly-2-hydroxypropyl-(pHEMA/pHPMA)-methacrylate backbone and terminal hydroxyl group. These polymers are members of the family of hydrophilic polymers that contain a covalent methacrylate backbone with a hydroxyl aliphatic side chain.

The application of methacrylates in wound care is not a new concept, as poly-2-hydroxyethyl-methacrylate in combination with polylethylene glycol 400 (PEG-400) was used as a burn dressing in the 1980s; however, the application process was difficult. First, liquid PEG-400 had to be sprayed on the wound, followed by atomising powder particles of hydrogel polymer, repeating the sequence until an integral film resulted.

Nathan et al. experimented by applying silver sulfadiazine on top of the intact dressing and were marginally successful in controlling the bacterial load at the wound surface without disrupting the dressing. Because the application method was very difficult to use in clinical practice, however, the material gradually disappeared from wound care during the subsequent years.

The today’s novel formulated methacrylate dressing overcomes previous problems and can be directly applied into a wound, transforming in presence of wound exudate, or, more interestingly in the context of wound antisepsis, with antimicrobial compounds. Because of the inert nature of the aggregated polymer whereby only the pHEMA/pHPMA – methacrylate particles react with each other, the methacrylate dressing can serve as a drug delivery matrix for various cationic and anionic wound antiseptics.

By using different antiseptics, it was demonstrated that a tailor-made and controlled antibacterial effect could be achieved using the same type of wound dressing (Figure 2).

In future, such concepts may allow the use of a wound dressing as a non-antimicrobial dressing, if antimicrobial action is not required.

It may also be used as an antimicrobial dressing to:
- Protect a non-infected wound from infection by loading it with 0.1% PHMB + 0.1% betaine
- Eradicate colonising microorganisms with 0.4% PHMB
- Treat infected wounds by rapid kill of pathogenic microorganisms with OCT or PVP-I

Following this algorithm, in future wound care managers may offer patients an individual, tailored wound treatment based on individual clinical demands.

<table>
<thead>
<tr>
<th>Ag+-dressing</th>
<th>Ag+ compound</th>
<th>Log-reduction (cfu/cm²)</th>
<th>V79 cytotoxicity (% cell growth inhibition)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S. aureus</td>
<td>P. aeruginosa</td>
<td></td>
</tr>
<tr>
<td>Hydrocolloid</td>
<td>Silver sulfadiazine 3.8</td>
<td>2.3</td>
<td>25%</td>
</tr>
<tr>
<td>Non-woven fabric A</td>
<td>Ionic silver 5.7</td>
<td>4.4</td>
<td>50%</td>
</tr>
<tr>
<td>Non-woven fabric B</td>
<td>Ionic silver 5.8</td>
<td>4.5</td>
<td>65%</td>
</tr>
<tr>
<td>Foam A</td>
<td>Silver sulphate 0.2</td>
<td>2.6</td>
<td>70%</td>
</tr>
<tr>
<td>Foam B</td>
<td>Nano-crystalline silver 1.2</td>
<td>-0.1</td>
<td>55%</td>
</tr>
</tbody>
</table>

Table 2. In-vitro parallel evaluation of antibacterial activity and cytotoxicity of different silver-based wound dressings. (modified based on Yunoki, Kohta, Ohyabu and Inoue, 2015)
Acknowledgement
This article was adapted from research originally published in the International Journal of Molecular Science, May 2013.
The present work was kindly supported by a research grant of the Foundation for Innovation and Education in Wound Management (FIEW).

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