22 Antiseptic Stewardship for Wound and Mucous Membrane Antiseptics

22.1 Composition and Intended Use

Wound and mucous membrane antiseptics can be based on different types of biocidal agents such as chlorhexidine digluconate, polihexanide, hydrogen peroxide, sodium hypochlorite, povidone iodine or octenidine dihydrochloride [1, 2]. In addition, silver may be used as an antimicrobial agent for wound treatment, e.g. in wound dressings. Most products contain a single biocidal agent.

They are used in health care, veterinary medicine and occasionally also in the domestic setting. Wound antiseptics are indicated for infected or critically colonized wounds [2]. Depending on a risk score, wound antiseptics may also be indicated for other types of wounds [2]. Mucous membrane antiseptics are typically applied prior to surgery, e.g. to the genitourinary or oral mucosa [3]. The summary below is an extract of previous book chapters on the biocidal agents.

22.2 Selection Pressure Associated with Commonly Used Biocidal Agents

22.2.1 Change of Susceptibility by Low-Level Exposure

The adaptive effects were classified as “no MIC increase”, “weak MIC increase” with a $\leq$4-fold MIC increase and “strong MIC increase” with a >4-fold MIC increase. The last category was divided into an unstable or stable MIC increase; sometimes the stability was unknown. A species may be found in two or more categories indicating that the adaptive response depends on the type of isolate. Most data on different adaptive effects caused by low-level exposure were found for chlorhexidine digluconate (78 species), polihexanide (55 species) and silver (20 species). Only few data were found for hydrogen peroxide (8 species), sodium hypochlorite (7 species), povidone iodine (5 species) and octenidine dihydrochloride (3 species).

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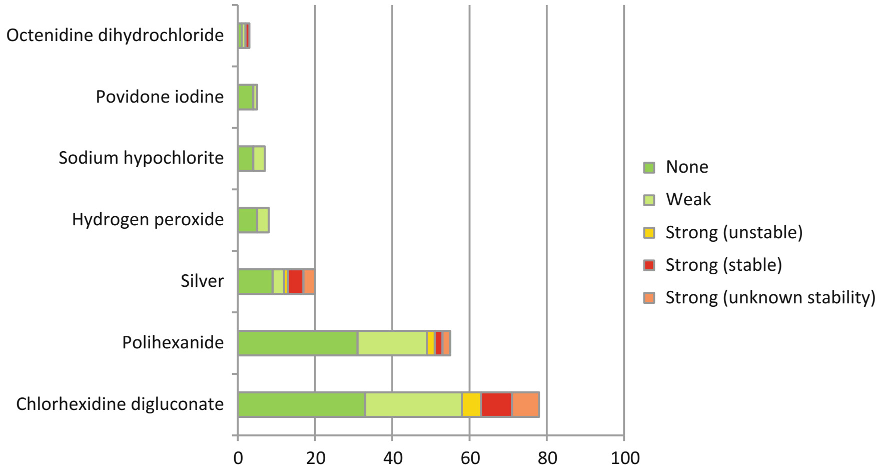

Fig. 22.1 Number of species with no, a weak or a strong adaptive MIC increase after low-level exposure to biocidal agents that may be found in wound or mucous membrane antiseptics

Figure 22.1 shows the distribution of adaptive response categories for the different biocidal agents. The majority of species did not show any MIC increase or only a weak MIC increase ($\leq$4-fold). A strong adaptive response was most frequently seen in silver (40%), chlorhexidine digluconate (26%) and polihexanide (11%). The strong MIC increase was stable in 50% (silver, mainly in sil-positive strains), 40% (chlorhexidine digluconate) and 33% (polihexanide) of species. With octenidine dihydrochloride, one species was found with a strong and stable adaptive response. Hydrogen peroxide, sodium hypochlorite and povidone iodine have so far not shown a strong MIC increase.

A strong and stable MIC increase after low-level exposure is probably the most critical adaptive response. Some species can be found in this group that have certainly a high relevance for infection control (Table 22.1). Most of them are among the Gram-negative species. It is noteworthy that the changes observed with polihexanide were rather moderate (5-fold–8-fold) and only found in Gram-positive species.

22.2.2 Cross-Tolerance to Other Biocidal Agents

Primarily chlorhexidine digluconate-tolerant isolates of *E. coli* and *S. Virchow* can be cross-tolerant to triclosan, isolates of *S. Tyhimurium* can be cross-tolerant to benzalkonium chloride, and isolates of *A. baylyi* can be cross-tolerant to hydrogen peroxide. Isolates of primarily octenidine dihydrochloride-tolerant *P. aeruginosa* can be cross-tolerant to chlorhexidine digluconate. Isolates of primarily sodium hypochlorite-tolerant *E. coli* can be cross-tolerant to hydrogen peroxide, and in *L. monocytogenes* cross-tolerance to benzalkonium chloride, another quaternary

Table 22.1 Bacterial species with a strong (>4-fold MIC increase) and stable adaptive response after low-level exposure to selected biocidal agents sometimes found in wound or mucous membrane antiseptics

Biocidal agent	Bacterial species with a strong and stable adaptive MIC increase
Chlorhexidine digluconate	*E. coli* ($\leq$ 500-fold)
	S. marcescens ($\leq$ 128-fold)
	P. aeruginosa ($\leq$ 32-fold)
	K. pneumoniae ($\leq$ 16-fold)
	S. aureus ($\leq$ 16-fold)
Silver	*E. coli* (128-fold)[a]
	E. cloacae ($\geq$ 32-fold)[a]
	K. pneumoniae ($\geq$ 32-fold)[a]
	K. oxytoca ($\geq$ 16-fold)[a]
Polihexanide	*E. faecalis* (8-fold)
	S. aureus (8-fold)
	S. epidermidis (4.8-fold)
Octenidine dihydrochloride	*P. aeruginosa* ($\leq$ 32 fold)

[a]Mainly sil-positive isolates or strains

ammonium compound and alkylamine can occur. Isolates of primarily hydrogen peroxide-tolerant *E. coli* can be cross-tolerant to aldehyde, and isolates of primarily hydrogen peroxide-tolerant *S. cerevisiae* can be cross-tolerant to ethanol. No cross-tolerance to other biocidal agents has been reported for povidone iodine and polihexanide.

22.2.3 Cross-Tolerance to Antibiotics

Povidone iodine, sodium hypochlorite, hydrogen peroxide and polihexanide have so far never been described with a cross-tolerance to antibiotics. A cross-tolerance between both silver and chlorhexidine digluconate and selected antibiotics can occur in numerous species. Cross-tolerance between octenidine dihydrochloride and selected antibiotics can occur in *P. aeruginosa*.

22.2.4 Efflux Pump Genes

Transporter and efflux pump genes were up-regulated after chlorhexidine digluconate exposure in *B. fragilis* and *B. cepacia complex*.

22.2.5 Horizontal Gene Transfer

Horizontal gene transfer can be successfully induced by chlorhexidine digluconate in *E. coli* (sulphonamide resistance by conjugation).

22.2.6 Antibiotic Resistance Gene Expression

In a vanA *E. faecium*, chlorhexidine digluconate was able to induce a ≥ 10-fold increase of vanHAX encoding VanA-type vancomycin resistance.

22.2.7 Other Risks Associated with Biocidal Agents in Wound and Mucous Membrane Antiseptics

Other risks may also be relevant in wound and mucous membrane antiseptics. They are not covered here in detail. Local tolerability including its possible toxic effect on cartilage, any favorable or negative effect on wound healing, its efficacy in the presence of organic load, the potential for sensitization and any systemic risk should also be evaluated [2].

22.3 Effect of Commonly Used Biocidal Agents on Biofilm

22.3.1 Biofilm Development

Typical biocidal agents in wound and mucous membrane antiseptics show a different effect on biofilm development (Fig. 22.2). For silver, often as nanoparticles, biofilm formation can be inhibited in *C. parapsilosis*, *C. tropicalis*, *C. albicans*, *E. coli*, *P. fluorescens*, *S. epidermidis* and *S. aureus*. Similar results are found for povidone iodine with an inhibition of biofilm formation in four species: *E. faecalis*, *S. aureus*, *S. epidermidis* and *C. albicans*. A decrease of biofilm formation was described for octenidine dihydrochloride but only at concentrations of $\geq 0.31\%$ which has no relevance in wound and mucous membrane antiseptics. Chlorhexidine digluconate exposure resulted in a decrease of biofilm formation in the majority of species. Sodium hypochlorite and hydrogen peroxide can rather enhance than inhibit biofilm formation. No data were found for polihexanide.

22.3.2 Biofilm Fixation

No data were found to assess the biofilm fixation potential of octenidine dihydrochloride, silver, chlorhexidine digluconate, povidone iodine, polihexanide, sodium hypochlorite or hydrogen peroxide.

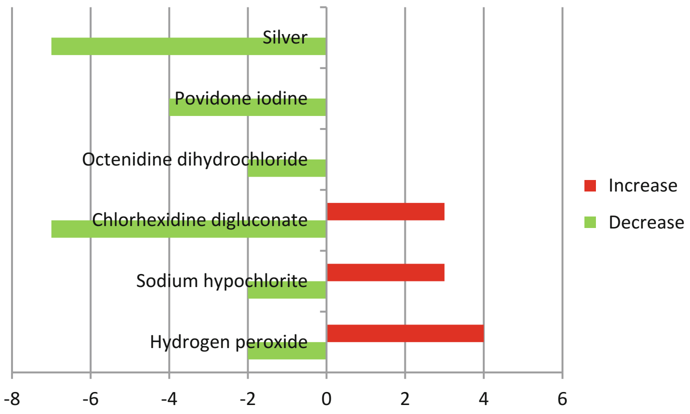

Fig. 22.2 Number of species with a decrease or increase of biofilm formation caused by biocidal agents that may be found in wound or mucous membrane antiseptics

22.3.3 Biofilm Removal

Povidone iodine has so far only been described with a strong biofilm removal. Silver, sodium hypochlorite and hydrogen peroxide have a mostly moderate biofilm removal capacity. Octenidine dihydrochloride could equally show a poor, moderate and strong biofilm removal. It is poor or moderate with polihexanide and chlorhexidine digluconate (Fig. 22.3).

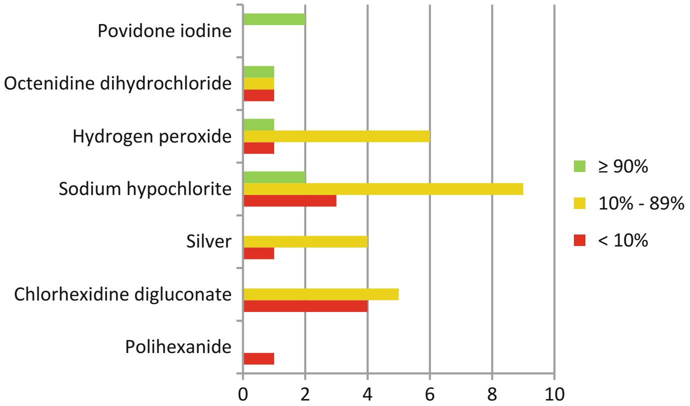

Fig. 22.3 Number of species with a strong (≥ 90%), moderate (10–89%) or poor biofilm removal (<10%) by biocidal agents that may be found in wound or mucous membrane antiseptics

22.4 Health Benefits of Biocidal Agents in Wound and Mucous Membrane Antiseptics

For patients with wounds, a health benefit is already the prevention of a wound infection, e.g. after soft tissue traumatic injuries or in wounds after cardiothoracic surgery. There is some evidence for polihexanide and sodium hypochlorite to suggest that a targeted antiseptic wound treatment is able to reduce infection rates [2]. The use of mucous membrane antiseptics is recommended prior to surgery for prevention of surgical site infections, e.g. in urology, gynaecology or ophthalmology [3].

22.5 Antiseptic Stewardship Implications

A low adaptive response in combination with a frequently observed inhibition of biofilm formation and a rather strong removal of existing biofilm can be attributed only to povidone iodine. Sodium hypochlorite and hydrogen peroxide also revealed a low adaptive response but can enhance biofilm formation in a few more species and have only a moderate biofilm removal capacity. Limited data with octenidine dihydrochloride suggest an inconsistent adaptive effect and also an inconsistent effect on biofilm removal. Polihexanide can exhibit a strong adaptive response which is in comparison to other biocidal agents quite low (5-fold to 8-fold) and only described in Gram-positive species. Its biofilm removal capacity is poor. Chlorhexidine digluconate and silver may both show quite frequently a strong adaptive response mainly among Gram-negative species. The effect caused by silver depends largely on the presence of sil-genes in the strains. Silver can inhibit biofilm formation where the effect of chlorhexidine digluconate is inconsistent. For biofilm removal, silver nanoparticles have mostly a moderate effect, whereas the effect of chlorhexidine digluconate is mostly poor.

The indication for wound or mucous membrane antiseptics depends on multiple factors and can not only rely on the potential for selection pressure. Nevertheless, povidone iodine seems to exhibit the lowest selection pressure and chlorhexidine digluconate the highest one.

References

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