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OCTENIDINE DIHYDROCHLORIDE – ANTIMICROBIAL ACTIVITY, ADAPTATION AND CLINICAL APPLICATION

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Abstract: Octenidine dihydrochloride (OCT) is an antiseptic used for the prevention of wound infections, treatment of wounds and for treating oral infections. The spectrum of OCT's activity includes Gram-positive and Gram-negative bacteria, as well as fungi, including multidrug-resistant (MDR) strains. For most species, it exhibits activity at concentrations ranging from approximately 1 to several µg/mL. OCT also exhibits strong antibiofilm activity, both against biofilm formation and mature biofilms. The compound has limited virucidal and antiparasitic activity. The Clinical Efficiency of MIC (CEMIC) index for most pathogens is classified as excellent, meaning that the MIC is much lower than the clinical concentration. The required contact time for OCT microbicidal action is fast, at just 1 minute. The possibility of adaptation to OCT has been described; however, the Karpinski Adaptation Index (KAI) for most species is below 0.2, indicating a very low or low risk of developing clinical resistance. Only in some isolates of *Proteus mirabilis* and *Pseudomonas aeruginosa* the risk of resistance development considered moderate. According to guidelines (Statement of the Polish Wound Management Association, German Consensus on Wound Antisepsis, and International Consensus Document "Use of wound antiseptics in practice"), OCT is the first-choice antiseptic for critically colonized wounds, infection-prone wounds, burns, wounds colonized by multidrug-resistant (MDR) pathogens or infected wounds, and for the prevention of surgical site infections (SSI). OCT is also used in umbilical stump care, the treatment of oral infections, skin and mucosal candidiasis, and bacterial vaginosis.

Keywords: anti-infective agents; antimicrobial stewardship; biofilm; nosocomial infection; wound infection; wound healing;

1. Introduction

A growing concern is the increasing number of individuals with wounds. It is estimated that approximately 1–2% of people worldwide experience chronic wounds (Sharma et al. 2024). An additional threat is the rise of multidrug-resistant (MDR) bacterial and fungal strains, leading to therapeutic failure and becoming a serious crisis (Bharadwaj et al. 2022; Bonomo et al. 2024). According to the latest guidelines (Nair et al. 2023; Sopata et al. 2023) antibiotics should be preserved, and antiseptics should be used for wound prevention and treatment. Antiseptics are antimicrobial agents that act at various levels: on the wound surface, in exudate, within the dressing structure, and in tissues. One such antiseptic is octenidine.

Octenidine dihydrochloride (OCT) is a cationic compound, stable within a pH range of 1.6–12.2 (Hübner et al. 2010). It has PubChem CID 51167, its molecular weight is 623.8 g/mol, and molecular formula $C_{36}H_{64}Cl_2N_4$ (PubChem). It exhibits strong antimicrobial activity, including effectiveness against Gram-pos-

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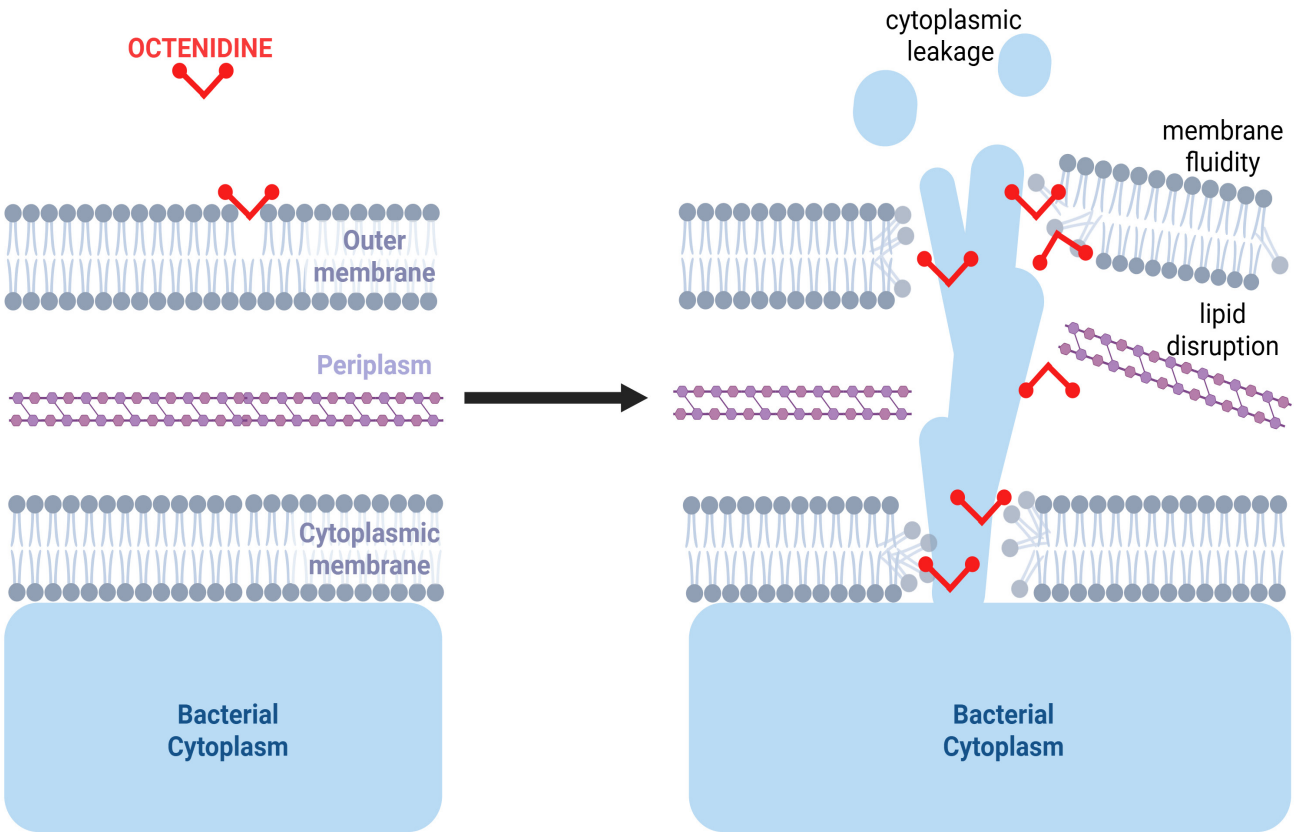
itive and Gram-negative bacteria, fungi, some viruses, and protozoa, while maintaining low cytotoxicity. OCT was introduced into medical practice over 25 years ago and is currently used in washing lotions, mouth rinses, oral tablets, and skin disinfectants.

2. Mode of action

OCT interacts with bacterial polysaccharides and enzymatic systems, leading to cytoplasmic leakage and disruption of essential cellular functions (Hübner et al. 2010). Unlike antibiotics that target specific cellular components, OCT exerts its antimicrobial effect by destabilizing the cell structure, compromising membrane integrity, disrupting the lipid bilayer, and increasing membrane permeability (Vejzovic et al. 2022). Additionally, it neutralizes the bacterial surface charge, causing the outer membrane to rupture and the cell wall to degrade. Once inside the periplasmic space, OCT reaches the inner membrane, where it induces lipid disruption, leading to depolarization and changes in membrane fluidity (Figure 1) (Malanovic et al. 2020). In *Candida* species, OCT has been shown to inhibit filamentation by interfering with ergosterol biosynthesis and compromising membrane integrity (Fang et al. 2023). Since its mechanism of action does not rely on lipid specificity, it is effective against a broad range of bacteria and fungi, including MDR strains (Malanovic et al. 2022). Due to its nonspecific mode of action, which involves membrane disruption, the likelihood of resistance development is considered minimal, and no cases of OCT resistance have been reported in clinical practice (Malanovic et al. 2020).

Figure 1. Mode of action of octenidine dihydrochloride. Created using the BioRender.com.



3. Antimicrobial activity

OCT exhibits a strong antibacterial effect (Koburger et al. 2010; Dydak et al. 2021; Krasowski et al. 2021; Loose et al. 2021; Denkel et al. 2022; da Silva et al. 2023). However, it has no effect on bacterial spores (Bigliardi et al. 2017). The minimal inhibitory concentrations (MIC) for most tested bacteria range from below 1 μg/mL to approximately 10 μg/mL (Table 1). However, for single strains of *Streptococcus pneumoni-*

ae and *Pseudomonas aeruginosa*, the maximum MIC values are significantly higher, at 32 μg/mL and 80 μg/mL, respectively. Fungi show similar susceptibility to OCT, with MIC values ranging from approximately 0.5 to 4 μg/mL. These MIC levels indicate that the antiseptic is effective at similar concentrations across different species. Comparable inhibitory concentrations of OCT have also been observed in MDR strains such as New Delhi metallo-β-lactamase-positive (NDM) *Enterobacter cloacae*, *Klebsiella pneumoniae* NDM, and *Candida auris* (Karpiński et al. 2025a). Additionally, for all MIC results, the Clinical Efficiency of MIC (CEMIC) index was analyzed, which represents the ratio of MIC values to clinical concentrations (Karpiński, et al. 2025b). The lowest clinical concentration of OCT used is 500 μg/mL. CEMIC is classified as excellent for values < 0.1, moderate for values between 0.1 and 0.9, and poor for values > 0.9 (Karpiński, et al. 2025b). For most species listed in Table 1, CEMIC was classified as excellent, meaning the MIC is much lower than the clinical concentration. This is particularly important for antiseptics, which, for example, may become diluted in wounds due to exudate or blood. In the case of OCT, even significant dilution within the wound does not reduce its activity. However, for some *P. aeruginosa* strains, CEMIC was classified as moderate.

Table 1. Minimal inhibitory concentrations (MIC) of octenidine against bacteria and fungi using microdilution method.

Microorganisms	Range of MICs (μg/mL)	Methodological remarks (medium type, colony counts, incubation time, and temperature)	References
Gram-positive bacteria			
Clostridium perfringens	1	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
Enterococcus faecalis	4	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
E. faecium	0.49-1.95	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
E. hirae	0.6-10	TSB, 10^8-10^9 cfu/mL, 24-72 h, no data	(Schug et al. 2022)
Staphylococcus aureus	2	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	0.49-0.98	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	2-4	SCS, 1.5-5×10^5 cfu/mL, 48 h, 37°C	(Denkel et al. 2022)
	0.9	MHB, 10^5 cfu/mL, 24 h, 37°C	(Krasowski et al. 2021)
	0.3-5	TSB, 10^8-10^9 cfu/mL, 24-72 h, no data	(Schug et al. 2022)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Methicillin-resistant *S. aureus* (MRSA)	1	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	1-4	MHB, 5×10^5 cfu/mL, 24-48 h, 37°C	(Dittmann et al. 2019)
S. epidermidis	0.49-7.8	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
Coagulase-negative staphylococci	2-4	SCS, 1.5-5×10^5 cfu/mL, 48 h, 37°C	(Denkel et al. 2022)
Streptococcus pneumoniae	8-32	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
S. pyogenes	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Gram-negative bacteria			
Acinetobacter baumannii	0.25-3.9	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
Enterobacter cloacae	3.9	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)

Escherichia coli	2	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	1.95-3.9	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	2-4	SCS, 1.5-5×10^5 cfu/mL, 48 h, 37°C	(Denkel et al. 2022)
	1.95-3.9	MHB or artificial urine, 10^5-10^6 cfu/mL, 20 ± 2 h, 37°C	(Loose et al. 2021)
	1-4	MHB, 10^6 cfu/mL, 20 ± 2 h, 37°C	(da Silva et al. 2023)
	0.6-20	TSB, 10^8-10^9 cfu/mL, 24-72 h, no data	(Schug et al. 2022)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Haemophilus influenzae	1	MHB 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
Klebsiella spp.	2-4	SCS, 1.5-5×10^5 cfu/mL, 48 h, 37°C	(Denkel et al. 2022)
K. pneumoniae	1.95-7.8	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Proteus mirabilis	1.95-3.9	MHB or artificial urine, 10^5-10^6 cfu/mL, 20 ± 2 h, 37°C	(Loose et al. 2021)
	3.125-6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Pseudomonas aeruginosa	2-8	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	3.9-15.7	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	8-32	SCS, 1.5-5×10^5 cfu/mL, 48 h, 37°C	(Denkel et al. 2022)
	2.25±0.95	MHB, 10^5 cfu/mL, 24 h, 37°C	(Krasowski et al. 2021)
	3.9-7.8	MHB or artificial urine, 10^5-10^6 cfu/mL, 20 ± 2 h, 37°C	(Loose et al. 2021)
	3.91-15.63	TSB, 10^5 cfu/mL, 24 h, 36°C	(Karpiński, et al. 2025b)
	1.25-80	TSB, 10^8-10^9 cfu/mL, 24-72 h, no data	(Schug et al. 2022)
	3.125-12.5	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Salmonella enterica	6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Shigella flexneri	6.25-12.5	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Yersinia enterocolitica	6.25	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Fungi			
Ascophera apis	0.78-3.125	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Candida albicans	1	MHB, 10^5 cfu/mL, 24-48 h, 36°C	(Koburger et al. 2010)
	0.49-0.98	TSB, 10^5 cfu/mL, 24 h, 37°C	(Dydak et al. 2021)
	0.45	RPMI with 2% glucose, 10^5 cfu/mL, 24 h, 37°C	(Krasowski et al. 2021)
	0.5 ± 0.25 and 0.9 ± 0.4	TSB, 10^6 cfu/mL, 24 h, 36°C	(Korbecka-Paczkowska and Karpiński 2024)
	1.95-3.91	Sabouraud broth, 10^6 cfu/mL, 24 h, 36°C	(Karpiński et al. 2024)
	0.78-1.56	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
C. auris	3.125	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
C. glabrata	0.78-3.125	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
C. tropicalis	0.78-1.56	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Cryptococcus neoformans	3.125	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)
Rhodotorula mucilaginosa	3.125	TSB, 10^5 cfu/mL, 24-48 h, 37°C	(Karpiński, et al. 2025a)

Abbreviations: MHB - Mueller–Hinton broth, TSB - Tryptic soy broth, SCS - Soybean casein solution, RPMI – Roswell Park Memorial Institute medium

OCT has limited virucidal activity, and the number of studies on this topic is scarce (Bigliardi et al. 2017). One of the studies reported that 0.1% concentration may be effective against coliphages f2 and MS2, as well as hepatitis B and herpes simplex viruses, but not against phages PhiX174 and adenoviruses (Hübner et al. 2010). The authors suggest that OCT exhibits virucidal activity only against enveloped viruses. However, there is a lack of recent studies confirming this effect.

The COVID-19 pandemic prompted several studies on the effect of OCT against SARS-CoV-2. In one study, using EN 14476 guidelines, a significant viral titre reduction was observed after 15 seconds of contact (Steinhauer et al. 2021). Another study showed that rinsing the mouth with OCT for one minute reduced SARS-CoV-2 RNA in saliva to undetectable levels by RT-qPCR (Smeets et al. 2022). However, both studies used Octenisept, which contains 0.1% OCT and 2% phenoxyethanol (PE). Since PE also has antimicrobial properties, it is difficult to attribute the antiviral effect solely to OCT. This is supported by a study where a product with 0.05% OCT but no PE showed weak activity against SARS-CoV-2 (Meister et al. 2020).

The antiparasitic effect of OCT has been described in relation to *Trichomonas vaginalis*. A combination of 0.1% OCT and 2% PE, demonstrated 50% effective concentration (EC50) values after 5 minutes of exposure at concentrations ranging from 5.7 to 21.4 µg/mL, and after 30 minutes at concentrations of 0.68 to 2.1 µg/mL (Küng et al. 2016). However, as with viruses, it remains unclear whether the anti-*Trichomonas* activity is primarily due to OCT, PE, or a combination of both.

4. Antibiofilm activity

OCT exhibits strong antibiofilm activity, both against biofilm formation and mature biofilm. Most studies show that complete biofilm reduction occurs within 24 hours, regardless of the microbial species (Rembe et al. 2020; Dydak et al. 2021; Krasowski et al. 2021; Loose et al. 2021). Only one publication showed that OCT requires up to 3 days for biofilm formation inhibition of *E. coli* (Loose et al. 2021). Table 2 demonstrates that the OCT concentrations required for antibiofilm activity are lower for Gram-positive bacteria than for Gram-negative bacteria. In the case of *C. albicans*, the data are inconclusive. There are publications describing the effect of OCT on bacterial viability in biofilms and biofilm reduction. Unfortunately, these data are very diverse. In some studies, OCT destroys 100% of the biofilm already at concentrations <100 µg/mL (Dydak et al. 2021; Krasowski et al. 2021), while in others, even a concentration of 1000 µg/mL does not destroy the entire biofilm (Davis et al. 2017; Rembe et al. 2020; Korbecka-Paczkowska and Karpiński 2024). It was also confirmed that OCT leads to the destruction of MRSA biofilm structure *in vivo* in mice (Huang et al. 2021). However, there is a lack of studies investigating its effect on the biofilm matrix in a short time. This would be important due to the short, usually only a few minutes long, application of OCT-containing products, such as oral mouthwashes or wound liquids.

Table 2. Antibiofilm activity of octenidine dihydrochloride.

Microorganism	Tested concentrations (µg/mL)	Time of action	% of biofilm reduction	Type of antibiofilm study	Reference
E. faecium	15.7-31.3	24 h	100	mature biofilm reduction	(Dydak et al. 2021)
S. epidermidis	15.7-125	24 h	100		(Dydak et al. 2021)
S. aureus	62.5	24 h	100		(Dydak et al. 2021)
	~50	24 h	100		(Krasowski et al. 2021)
	1000	24 h	~85%		(Rembe et al. 2020)
MRSA	1000	3 days	80%		(Davis et al. 2017)
A. baumannii	7.8-250	24 h	100		(Dydak et al. 2021)
E. coli	250	3 days	100	biofilm formation inhibition	(Loose et al. 2021)
	125-500	24 h	100	mature biofilm reduction	(Dydak et al. 2021)
E. cloacae	250-500	24 h	100		(Dydak et al. 2021)
K. pneumoniae	62.5-500	24 h	100		(Dydak et al. 2021)

P. mirabilis	250	24 h	100	biofilm formation inhibition	(Loose et al. 2021)
P. aeruginosa	500	24 h	100		(Loose et al. 2021)
	250 to >500	24 h	100	mature biofilm reduction	(Dydak et al. 2021)
	~180	24 h	100		(Krasowski et al. 2021)
	1000	24 h	~100		(Rembe et al. 2020)
C. albicans	500	24 h	47 ± 11		(Korbecka-Paczkowska and Karpiński 2024)
	1000	24 h	51 ± 13		(Korbecka-Paczkowska and Karpiński 2024)
	15.7-31.3	24 h	100		(Dydak et al. 2021)
	~60	24 h	100		(Krasowski et al. 2021)

5. Bactericidal time

According to the European Standard EN 1040:2005, an effective antiseptic should achieve a 5-log as below reduction of a given bacteria (European Standard EN 1040:2005). This corresponds to a 99.999% reduction in pathogen count. Studies indicate that pure OCT at a concentration of 500 μg/mL reduced the planktonic form of *P. aeruginosa* by over 5-log within 1 minute (Karpiński, et al. 2025b). In other studies, a significant reduction of *C. albicans*, *S. aureus*, and *P. aeruginosa* also required a contact time of 1 minute and OCT concentrations ranging from 10 to 50 μg/mL (Koburger et al. 2010). This contact time is shorter for the OCT/PE combination, e.g. for Octenisept with 1000 μg/mL of OCT. The contact time required for total inhibition of *S. aureus*, *E. faecalis*, and *C. albicans* is only 15 seconds, for this product. For a 50% solution, the contact time for *E. faecalis* and *C. albicans* increased to 3 minutes (Tirali et al. 2009). OCT/PE achieves a 5 $\log_{10}$ CFU/mL reduction within 1 minute against *P. aeruginosa* and *S. aureus* under standard conditions (EN 13727), in the presence of wound exudate, as well as in a modified peptide challenge test (Severing et al. 2022). Studies conducted in accordance with EN 13727:2012+A1 demonstrated that OCT at a concentration of 100 μg/mL achieves a reduction of >5 $\log_{10}$ within 1 minute for isolates of *A. baumannii*, *E. cloacae*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. This activity was observed in three types of media: without organic load, with albumin, and with albumin and erythrocytes (Alvarez-Marin et al. 2017). Some papers indicate that OCT may be less effective in the presence of organic material (Schedler et al. 2017; Barreto et al. 2020). Schedler et al. (2017) showed that, for 1000 μg/mL OCT, the time required for reduction of microorganisms by ≥ 5 $\log_{10}$ in the presence of organic soil can lasts from 3 h to 24 h.

Contact time in biofilm conditions needs to be extended. After 30 minutes of 500 μg/mL OCT exposure, 66.6% of *C. albicans* cells within the biofilm remain viable, while complete eradication occurs only after 1 hour. For *S. aureus* and *P. aeruginosa*, 66.6% of bacteria remain viable after 15 minutes, 55.5% after 30 minutes, and complete killing is achieved after 24 hours (Krasowski et al. 2021). In other studies, the OCT/PE combination eradicated bacterial viability in mature *P. aeruginosa* biofilm by 46% within 15 minutes and 100% within 30 minutes, while *S. aureus* was completely eradicated within 1 minute (Junka et al. 2014). The faster action may be associated with the additional presence of PE.

6. Adaptation to OCT

Adaptation to antiseptics is a process in which bacteria and/or fungi gradually increase their tolerance to a given antiseptic after repeated or prolonged exposure (Verspecht et al. 2019). This adaptation often leads to the ability of microorganisms to grow at increasing concentrations of antiseptics. In contrast to classical antibiotic resistance, adaptation to antiseptics usually does not result from the acquisition of resistance genes but rather from mechanisms such as biofilm formation, metabolic changes and growth retardation, alterations in cell membrane structure, and active removal of the antiseptic from the cell *via* efflux pumps (Verspecht et al. 2019; Wand et al. 2019; Bock et al. 2021). Wand et al. (Wand et al. 2019) described the efflux pump SmvA and membrane remodeling as responsible for OCT tolerance in *K. pneumoniae*. Additionally, it was observed that adaptation to chlorhexidine may lead to decreased susceptibility to other cationic bio-

cides, including OCT. Tolerance associated with the efflux pump has been linked to mutations in phosphatidylserine synthase *pssA* and phosphatidylglycerolphosphate synthase *pgsA* (Bock et al. 2021). In another study, opposite conclusions were drawn, demonstrating that Gram-positive bacteria carrying genes encoding efflux pumps contribute to antimicrobial resistance but do not affect sensitivity to low concentrations of OCT (Conceição et al. 2019). The results of studies on adaptation to OCT are varied. Table 3 shows that some studies found no development or only low tolerance to OCT in strains such as *S. aureus, S. epidermidis, Citrobacter* spp., and *Enterobacter* spp. (Nicolae Dopcea et al. 2020; Garratt et al. 2021; Karpiński 2024). However, other publications confirmed the development of adaptation to OCT, particularly in *P. mirabilis* and *P. aeruginosa* (Shepherd et al. 2018; Garratt et al. 2021; Pelling et al. 2024). The Karpinski Adaptation Index (KAI) is used in studies to assess the potential risk of developing resistance to antiseptics (Karpiński 2024). For most strains listed in Table 3, the KAI is below 0.2, indicating that the level of adaptation is significantly lower than the clinical concentration. Therefore, these strains have a very low or low risk of developing clinical resistance to OCT. Only in some isolates of *P. mirabilis* and *P. aeruginosa* does the risk of resistance development increase to a moderate level (Table 3).

Table 3. Results of studies on the development of microorganism adaptation to OCT.

Microorganism	Initial MIC (before adaptation) (µg/mL)	MIC after adaptation (µg/mL)	Fold increase in adaptation relative to initial MIC	Reference	Karpinski Adaptation Index (KAI)	Risk of clinical resistance to OCT
S. aureus	2	4.5	× 2.25	(Karpiński 2024)	0.009	Very low
S. epidermidis	0.2	0.49	× 2.45	(Nicolae Dopcea et al. 2020)	0.00098	Very low
Citrobacter spp.	2	2	× 1	(Garratt et al. 2021)	0.004	Very low
Enterobacter spp.	4	4-8	× 1-2	(Garratt et al. 2021)	0.008-0.016	Very low
P. mirabilis	2	128	× 64	(Pelling et al. 2024)	**0.256**	Moderate
	8	16	× 2	(Tagliaferri et al. 2024)	0.032	Very low
P. aeruginosa	7.8–15.6	50-75	× 3.2–12.8	(Karpiński, et al. 2025b)	0.12	Low
	4	32-64	× 8-16	(Garratt et al. 2021)	0.064-0.128	Very low/Low
	32	256	× 8	(Tagliaferri et al. 2024)	**0.512**	Moderate
	4-8	32-128	× 4-32	(Shepherd et al. 2018)	0.064-**0.256**	Very low/ Moderate
C. albicans	1.95-3.9	7.5-10	× 1.9-5.1	(Karpiński et al. 2024)	0.019	Very low

Interpretation of the Karpinski Adaptation Index: KAI ≤ 0.1: very low risk of clinical resistance; 0.1 < KAI ≤ 0.2: low risk of clinical resistance; 0.2 < KAI ≤ 0.8: moderate risk of clinical resistance; 0.8 < KAI < 1.0: high risk of clinical resistance; KAI ≥ 1.0: very high risk of clinical resistance (Karpiński 2024).

7. Precautions and application of OCT

OCT meets the criteria for selecting antimicrobial products in the wound healing process, namely:

- it has broad-spectrum antimicrobial effectiveness and a fast action time,
- it has the ability to destroy biofilm,
- it has tissue tolerance, lacks cytotoxicity and carcinogenicity,
- it can be combined with surfactants and specialized dressings,
- it does not lead to the development of resistance,
- it is not inactivated by protein loads and pH changes (Kramer et al. 2018).

OCT-based products are recommended for wound prevention and treatment. Combinations such as 0.1% OCT + 2% PE or 0.05% OCT + ethylhexylglycerin are approved. Contraindications for using OCT products include: peritoneal lavage, fistulas, and other structures from which the applied substance cannot be thoroughly rinsed; use in the extraperitoneal space; use on hyaline cartilage and central nervous system structures; and allergy. OCT rarely causes side effects. Documented effects include blistering, necrosis, and scarring in

newborns (Biermann et al. 2016), contact dermatitis, and swelling (Calow et al. 2009; Biermann et al. 2016). The use of OCT without drainage may lead to persistent edematous changes, inflammatory reactions, and necrosis (Eigner et al. 2023).

According to the International Consensus Document "Use of Wound Antiseptics in Practice" from 2023 (Nair et al. 2023), guidelines of Polish Wound Management Association (Sopata et al. 2023) and the German Consensus on Wound Antisepsis (Kramer et al. 2018), OCT is the first-choice antiseptic for critically colonized wounds, infection-prone wounds, burns, wounds colonized by MDR pathogens or infected wounds, and for surgical site infections (SSI) prevention. OCT is also used in umbilical stump care (Mivšek et al. 2017), treatment of skin and mucosal fungal infections (Novakov Mikić and Stojic 2015) and bacterial vaginosis (Swidsinski et al. 2015). OCT inhibits dental plaque formation and is used in treating oral inflammation and periodontitis. Thus, it is an effective alternative to chlorhexidine and other contemporary mouthwashes (Grover et al. 2021; Rath et al. 2024). However, all antiseptics, like antibiotics, particularly when used for long periods, may lead to oral and intestinal dysbiosis (Amaral et al. 2023; Brookes et al. 2023; Contaldo et al. 2023). It is important for future studies to investigate the long-term influence of antiseptics, including OCT on host microbiota and its implications for antimicrobial stewardship.

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Conflict of interest

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