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Review Article

REVIEW ARTICLE

The antiseptic Miramistin: a review of its comparative in vitro and clinical activity

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One sentence summary: Miramistin is a topical antiseptic that was developed within a framework of the Soviet Union Cold War Space Program; miramistin has a broad antimicrobial action, including activity against biofilms and a clinical profile showing good tolerability.

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ABSTRACT

Miramistin is a topical antiseptic with broad antimicrobial action, including activity against biofilms and a clinical profile showing good tolerability. Miramistin was developed within a framework of the Soviet Union Cold War Space Program. It is available for clinical use in several prior Soviet bloc countries, but barely known outside of these countries and there is almost no mention of miramistin in the English literature. However, considering emerging antimicrobial resistance, the significant potential of miramistin justifies its re-evaluation for use in other geographical areas and conditions. The review consists of two parts: (i) a review of the existing literature on miramistin in English, Russian and Ukrainian languages; (ii) a summary of most commonly used antiseptics as comparators of miramistin. The oral LD_{50} was 1200 mg/kg, 1000 mg/kg and 100 g/L in rats, mice and fish, respectively. Based on the results of the review, we suggest possible applications of miramistin and potential benefits over currently used agents. Miramistin offers a novel, low toxicity antiseptic with many potential clinical uses that need better study which could address some of the negative impact of antimicrobial, antiseptic and disinfectant resistance.

Keywords: miramistin; toxicity; Candida; MRSA; antimicrobial resistance

INTRODUCTION

Miramistin (myramistin), benzyl dimethyl [3- (myristoilamino) propyl] ammonium chloride, monohydrate, is a topical antiseptic that was developed in the Soviet Union during the Cold War within the framework of the 'Space Biotechnology Program'. The aim of the project was to develop an antiseptic for use in orbital satellite stations which had a broad spectrum of antimicrobial activity as well as being active against resistant isolates with low toxicity. After the screening of potential candidates, one compound was selected and given a code of 'BX-14'. As all of the

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work was done in the framework of a Space Program, all information on this compound was classified.

The information was declassified after the change of the political climate in the 1980's and this allowed the first preclinical research to take place. However, the economic decline of the Soviet Union in the 1980s hindered further development of miramistin. Research funding was stopped and research centers were split between newly emerging countries. Some research continued but it was performed only using available and inadequate resources. Due to the absence of a centralized research database and lack of inter-university communication, duplicate studies were performed without a cohesive overarching project plan.

Russian and Ukrainian academic papers are still poorly accessible. An electronic database of academic papers was only recently created but the majority of papers are still not included, therefore publications about miramistin are available only through Universities' catalogues, which are paper-based and cannot be searched via the internet.

The problem of AMR and a need for new antimicrobials

Resistance to antimicrobials has become a major problem across the world as it drastically reduces treatment options (Theuretzbacher 2017). Multidrug-resistant pathogens, namely carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant *Enterococci* (VRE) and *Candida auris* are of the major concern. *Candida auris* is an emerging pathogen associated with nosocomial outbreaks on five continents (Reyes, Bardossy and Zervos 2016; Biswal *et al.* 2017; Logan and Weinstein 2017) and carries substantial morbidity, mortality and healthcare costs. Antiseptics could play an important role in the prevention and control of such outbreaks (Abdolrasouli *et al.* 2017; Lowe *et al.* 2017; Musuuza *et al.* 2017; Jeffery-Smith *et al.* 2018). There is evidence that decontamination with antiseptics may reduce transmission of resistant pathogens (Daneman *et al.* 2013); other studies indicate that the use of antiseptics may prevent acquisition of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* (Huang *et al.* 2016).

As a result of a widespread use of antiseptics, resistance to antiseptics and disinfectants has emerged which includes antimicrobial cross-resistance (Bragg et al. 2014, 2018; Harbarth *et al.* 2014). There is therefore a need for novel antiseptics. Miramistin was used clinically in prior Soviet Bloc countries and has broad antimicrobial action including activity against biofilms (Danilova *et al.* 2017) [Данилова *et al.* 2017]. Miramistin is a 'novel' antiseptic for other geographies hence there is no evidence of acquired resistance to this compound in regions outside prior Soviet bloc countries, and is unlikely. Here we review its potential for use in other regions of the world and conditions.

Role of antiseptics in infection control and potential caveats

Antiseptics are one cornerstone of infection control, via decontamination of surfaces, hospital rooms and equipment. Existing antiseptics have limitations including acquired resistance and user toxicity, such as exacerbation of asthma in nurses (Dumas *et al.* 2017). Until the recent pandemic of COVID-19, the primary focus of hospital decontamination has been sterilisation after patients with *Clostridium difficile*, methicillin resistant *Staphylococcus aureus*, norovirus, multi-drug resistant bacteria and recently *C. auris*. Currently the focus has expanded to killing SARS CoV2 as this virus persists for hours and days on multiple surfaces (Kampf *et al.* 2020). Decontamination of endoscopy equipment is focussed on prevention of transmission of enteric bacteria and tuberculosis—glutaraldehyde is frequently used in this context. Several antiseptics are routinely incorporated into hand washing solutions, including alcohol and chlorhexidine, and it is generally assumed that all of these measures are highly effective in preventing transmission, but with few direct efficacy studies. It is not our intent to review all this literature here, but provide a backdrop for potential positioning of miramistin.

REVIEW OF EXISTING LITERATURE

Search strategy and selection criteria

A search was performed in PubMed and Google scholar (English) with the following search terms: 'miramistin', 'myramistin'. The search was performed in the following Russian and Ukrainian language databases 'elibrary.ru', 'cyberleninka', and 'Maksymovych Scientific Library'. The search covers the period from January 1990 to January 2020.

Mode of action of miramistin

Miramistin is a cationic detergent that exhibits antibacterial, antiviral and antifungal activity. Miramistin molecule is presented in the Fig. 1. The antimicrobial mode of action relies on an association between negatively charged phospholipids in microbial membranes and the positively charged nitrogen of miramistin, as with other quaternary ammonium compounds (QACs) (Wessels and Ingmer 2013). The hydrophobic tail of miramistin then penetrates the hydrophobic bacterial membrane with the consequent disruption of its physical and biochemical properties (Gilbert and Al-taae 1985; Ceragioli *et al.* 2010). Positively charged nitrogen remains on the outer surface and disrupts the normal charge distribution of the outer surface of the membrane (Ioannou, Hanlon and Denyer 2007). The interaction of miramistin with the cellular membrane results in: 1) the masking of cellular receptors, 2) disruption of the membrane, and, 3) ultimately, leakage of cellular content (Vieira and Carmona-Ribeiro 2006; Ioannou, Hanlon and Denyer 2007). At higher concentrations, miramistin can solubilize cellular membranes with the consequent formation of micellar aggregates (Friedrich *et al.* 2000; Gilbert and Moore 2005; Vieira and Carmona-Ribeiro 2006; Zhou *et al.* 2016). There is also a possibility that miramistin binds to microbial DNA (Zinchenko *et al.* 2004). The mechanism of action of miramistin is summarized in the Fig. 2.

Antifungal activity

Antifungal activity of miramistin has been poorly studied. The largest *in vitro* study of miramistin antifungal activity was done by Molochnoye *et al.* (2003); the results of this study are summarized in Table 1. In this study 101 clinical isolates belonging to 13 clinical important genera *(Aspergillus, Penicillium, Trichophyton, Epidermophyton, Microsporum, Stachybotrys, Ulocladium, Botrytis, Candida, Rhodotorula, Cryptococcus, Trichosporon, Malassezia)* were used (31 species in total). These isolates were collected during the period 1972–2003. The authors have used neither the Clinical and Laboratory Standards Institute (CLSI) nor the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, so, it is not possible to compare MIC results of miramistin with other antiseptics.

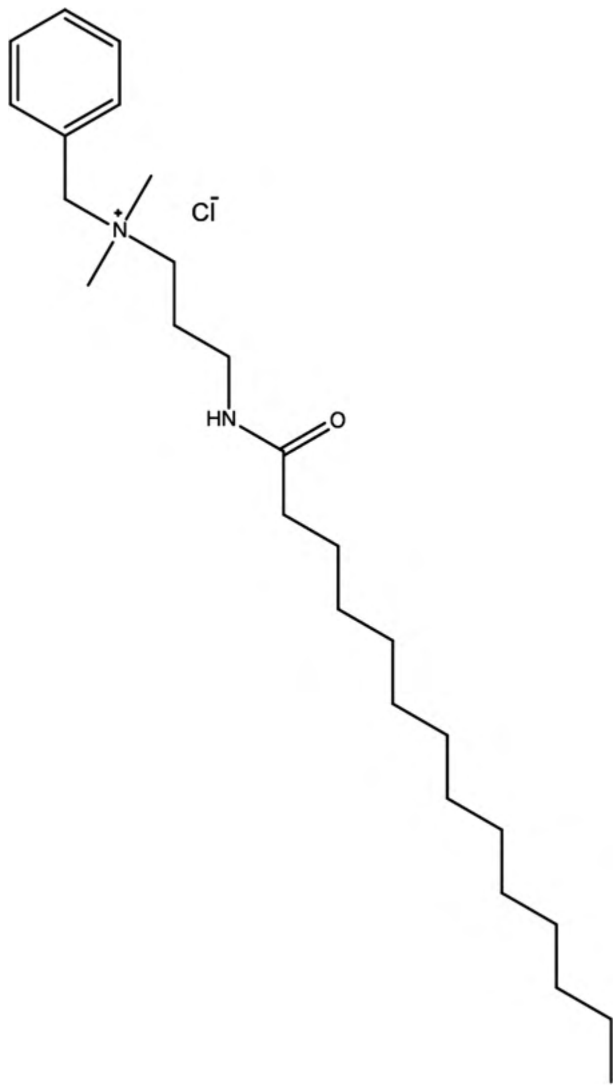

Figure 1. Miramistin molecule.

Another similar study (Dunayevskiy and Kirichenko 2013) [Дунаевский and Кириченко 2013] showed that miramistin demonstrated inhibitory properties against some fungi (*Trychophyton spp., Aspergillus spp., Penicillum spp., Candida spp., Rhodutorula spp., Torulopsis spp.)* at concentrations from 1–100 mg/L. The experiment was done on a smaller scale than the study outlined above but its methodology is apparently similar. The study by Arzumanian (2002) tested miramistin against basidiomycete yeasts (*Rhodotorula spp., Cryptococcus spp., Trichosporon* spp.). Ten antifungals from different groups were used as a comparison. The viability of the cultures was tested after 10 days of incubation with azole compounds. Miramistin showed the best *in vitro* activity.

A recent study by Kryvorutchenko (2010) used 22 clinical isolates of *Candida* spp. inoculated into 0.01% (100 mg/L) water solution of miramistin for 15, 45, and 60 minutes, followed by the viability cultures. The study showed that miramistin is fungicidal against the majority of *Candida* isolates, with some isolates killed after only 15 minutes of incubation with miramistin.

These studies show that miramistin has antifungal activity, but its antifungal activity cannot be compared with other antifungals and antiseptics based on these results, because none of these studies have used highly reproducible techniques.

We have studied (Osmanov, Wise and Denning 2019) antifungal activity of miramistin against antifungal resistant strains using CLSI antifungal susceptibility testing methodology. The range of MICs against fungi (*Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, *Penicillium* spp., *Mucorales* spp., *Neoscytalidium* spp., *Scedosporium* spp., *Alternaria alternata*, *Trichophyton* spp.) was 1.56–25 mg/L (GM 3.13 mg/L) (Table 2). Miramistin resistance was not found in the small number of strains tested per species. Miramistin exhibited equal activity against isolates that are susceptible and resistant to other antifungal agents; particularly miramistin is equally active against azole resistant *Candida* and *A. fumigatus* isolates, non-*fumigatus Aspergillus* species, including intrinsically amphotericin B resistant *A. terreus*; and rare and unusual species that are intrinsically resistant to azole and polyene antifungals such as *Neoscytalidium dimidiatum, Neoscytalidium dimidiatum* var. *hyalinum, Lomentospora. prolificans, S. apiospermum,* and *Alternaria alternata*. The limitations include few isolates tested, limited duplicate experiments and confirmatory tests. As the majority of isolates (>60%) were resistant or multi-drug resistant organisms, MICs for control drugs are significantly higher than the values that would have been obtained in a large study with random or sequential clinical isolates.

Antibacterial activity

Previous studies indicate that miramistin has a broad antibacterial spectrum. In the study by Vasil'eva *et al.* (1993), 236 bacterial strains were incubated with 100 mg/L solution of miramistin for 18 hours. After exposure only 9.3% of isolates remained viable. *Staphylococci* were the most resistant organisms. The study by Bitkova *et al.* (1995) [Биткова *et al.* 1995] investigated the activity of miramistin against *Staphylococcus aureus, P. aeruginosa, Proteus vulgaris,* and *Klebsiella pneumoniae*. The study found that all organisms were inhibited at a concentration of 25 mg/L.

In the study by Frovlova and Kosynets (2008) miramistin was compared to better-known antiseptics: chlorhexidine digluconate, dioxidine, potassium hydrochloride, furaginum, boric acid, furacilin and iodopiron. These antiseptics were tested against organisms that cause surgical infection. Miramistin and dioxidine were found to be the most potent, and the only antiseptics exhibiting high inhibitory activity against coagulase negative *Staphylococci*, *Proteus* spp., and *Pseudomonas aeruginosa*. Miramistin also suppresses the transfer of pathogenic plasmids of *E. coli* (Hly, Ent, F, and R) at sub-inhibitory concentrations alongside the disruption of conjugation pili and surface structures. However, miramistin does not eliminate pathogenic plasmids from the microorganisms (Krivoshein YuS *et al.* 1988).

Several studies were done to investigate antibacterial activity of miramistin against sexually transmitted pathogens (Kryvosheyn and Rud'ko 2003) [Кривошеин and Рудько 2003]. It was shown that, *in vitro,* miramistin is microbicidal against *Treponema pallidum, Trichomonas vaginalis and Neisseria gonorrhoeae*; benzalkonium chloride was used as a comparator..

Fromm-Dornieden *et al.* (2015) have studied antimicrobial activity of miramistin and cetylpyridinium chloride as components for wound dressing and investigated their activity against *S. aureus, P. aeruginosa* and *E. coli.* To determine antibacterial activity in suspension researchers have adapted and modified previously published quantitative suspension method (Koburger

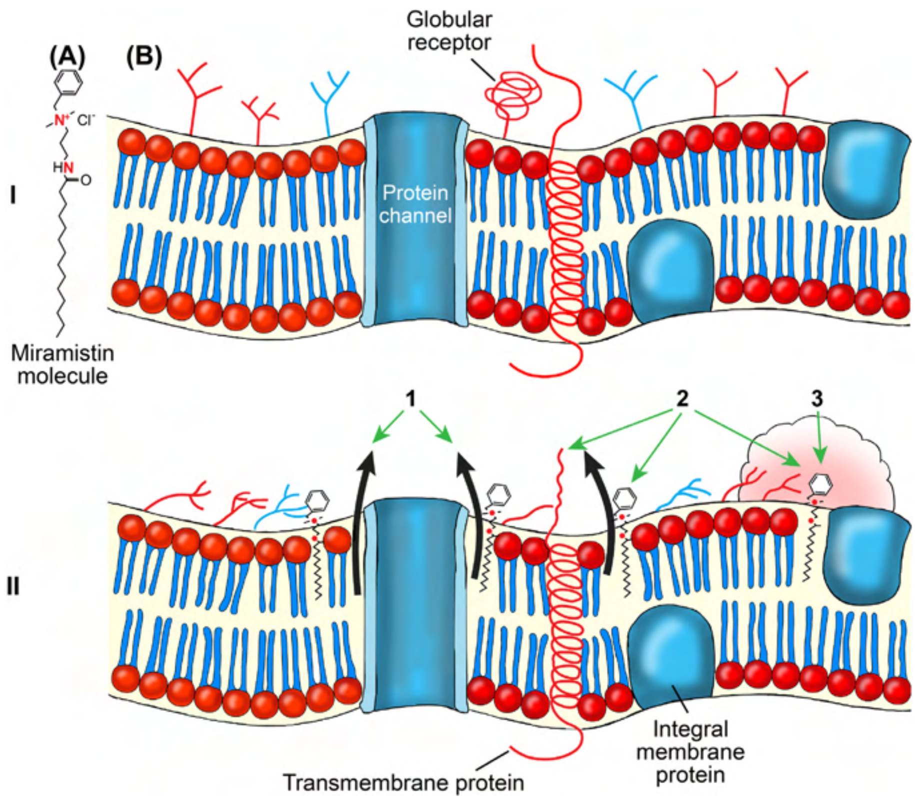

Figure 2. Mode of action of miramistin. (I) miramistin and normal membrane. **(A)** miramistin molecule and charge distribution (miramistin molecule is not in scale); **(B)** normal cellular membrane structure. (II) Interaction of miramistin with cellular membrane (miramistin molecule is approximately in scale to membrane): 1. Leakage of the membrane; 2. Alteration of the cellular receptors; 3. Alteration of normal charge distribution.

Table 1. A summary of fungal MICs Molochnoye *et al.* (2003).

Species	MIC range (mg/L)
Candida spp.	15 -100
Trichophyton spp.	100–500
T. mentagrophytes	30
Malassezia spp.	1000–5000
M. sympodialis	100–500
Rhodotorula spp.	1–60
Cryptococcus spp.	1–60
Trichosporon spp.	1–60

et al. 2010) based on German Institute for Standardisation methods (Deutsches Institut fur Normung 2005; Normung 2005). Miramistin was active against *S. aureus* at the concentration of 30 mg/L against *E. coli* at 125 mg/L and against *P. aeruginosa* at 500 mg/L, while cetylpyridinium chloride was active against *S. aureus* at the concentration of 30 mg/L, against *E. coli* at 250 mg/L and against *P. aeruginosa* at 5000 mg/L.

Miramistin can potentiate the effect of antibiotics by increasing the permeability of a microbial cell wall. (Fakher 1991; Milyavskiy *et al.* 1996) [Фахер 1991; Милявский *et al.* 1996]. *In vitro* data show that for β-lactam antibiotics it potentiates their effect up to 6-fold, and for other antimicrobials from 3.1 (levomycetin) to 64 times (polymyxin) (Fakher 1991; Milyavskiy *et al.* 1996; Dunayevskiy and Kirichenko 2013) [Фахер 1991; Милявский *et al.* 1996; Дунаевский and Кириченко 2013].

Antiviral activity

In vitro data suggest that miramistin is active against Influenza A, Human Papilloma Virus-1 and 2, coronaviruses, adenoviruses and Human Immunodeficiency Virus (Kryvorytchenko 1990; Kryvorytchenko *et al.* 1994; Dunaevskyy and Kyrychenko 2013) [Криворутченко 1990; Криворутченко *et al.* 1994; Дунаевский and Кириченко 2013]. There are some old data on miramistin activity for coronaviruses (Криворутченко 1990; Криворутченко *et al.* 1994; Дунаевский and Кириченко 2013) viruses, pertinent to the current pandemic.

Use of miramistin for impregnation of nanoparticles and medical devices

An anti-bacterial veterinary drug containing silver nanoparticles coated with miramistin was developed (Argumistin®) (Krutyakov *et al.* 2016). Promising clinical results in dogs suggest possible use of Argumistin® in humans but more research is required (Krutyakov *et al.* 2016). Miramistin is also suitable for impregnation into surgical sutures (Zhukovskii 2008); however, further clinical research is needed.

Toxicity of miramistin

Mutagenic activity was studied according to 'Evaluation and testing of drugs for mutagenicity: principles and problems, report of a WHO scientific group 1971 protocol' (1971) using histidine-dependent *S. tyhpimirium* from B. Ames collection. Results have shown that miramistin does not exhibits direct mutagenic properties (1993). Fromm-Dornieden *et al.* (2015) have

Table 2. MICs for fungal isolates (Osmanov, Wise and Denning 2019).

	Miramistin		Fluconazole		Itraconazole	
Strains	Range (mg/L)	GM (mg/L)	Range (mg/L)	GM (mg/L)	Range (mg/L)	GM (mg/L)
Candida yeasts	1.6–3.1	3.1	0.06–> 16	>16	0.03–> 0.5	0.25
C. neoformans	2.6–6.3	2.3	4–8	6	0.1–0.25	0.1
Moulds	6.3–25	10	0.3–> 16	>16	0.1–> 16	10.5
Rare/unusual species including intrinsically azole and polyene resistant strains	6.3–25	6.3	>16	>16	0.5–> 16	1

Table 3. A summary of chemical properties and patent data for antiseptics.

Antiseptic	Chemical Formula	Molecular Weight	LogP	tPSA	Filed Patent Dates (Past & Present)
Miramistin	$C_{26}H_{47}N_2O^+$	403.67	–	–	1990, 2005
Chlorohexidine	$C_{22}H_{30}Cl_2N_{10}$	505.45	4.76	177.58	1991, 1997, 2005
Triclosan	$C_{12}H_7Cl_3O_2$	289.54	4.86	29.46	1994, 2001, 2009
Benzalkonium chloride	$C_{19}H_{34}N^+$	276.49	–	–	2004
Decamethoxin	$C_{38}H_{74}N_2O_4{}^{2+}$	623.02	–	–	1996, 2016
Dioxidine	$C_{10}H_{10}N_2O_4$	222.20	–	86.84	2016
Taurolidine	$C_7H_{16}N_4O_4S_2$	284.35	– 1.9	98.82	2005, 2015
N-Chlorotaurine	$C_2H_6ClNO_3S$	159.58	–	66.4	2000

tested cytotoxicity of miramistin using murine fibroblasts and human keratinocyte cell lines. Miramistin has shown cytotoxic impact at concentrations of $> 8 \times 10^{-4}$, while cetylpyridinium chloride was toxic at concentrations $> 3 \times 10^{-3}$.

We have studied (Osmanov, Wise and Denning 2019) safety of miramistin using McCoy mammalian cell lines and miramistin was not toxic at concentration 1000 mg/L; while chlorhexidine was toxic at concentration 7.81 mg/L. As was shown by Svystov (2003) [Свистов 2003] miramistin acute oral toxicity (LD_{50}) in rats is 1200 mg/kg and 1000 mg/kg in mice, in fish is 100 g/L (2 hrs. of exposure); acute subcutaneous toxicity (LD_{50}) in rats is 670 mg/kg and 628 mg/kg in mice. In our study, miramistin did not show any acute systemic toxicity in *Galleria* at 2000 mg/kg.

Miramistin chronic toxicity

Chronic cutaneous toxicity was studied applying 0.1, 1.0 and 10 g/L solution to skin of rabbits and guinea pigs 5–7 times a week for 26 weeks. No skin reactions or changes in total white blood cell count or body weight were observed at any concentration (Svystov 2003) [Свистов 2003].

Miramistin mucosal toxicity

Toxicity of miramistin in the eye was studied by applying 0.1 g/L, 1 g/L and 10 g/L onto eyes of rabbits and guinea pigs once a day for 40 days. Miramistin was irritative at concentration of 10 g/L, but not at lower concentrations (Svystov 2003). Miramistin at a concentration of 0.1 g/L was instilled to the dog's urethra for 10 days. No changes in urinalysis were observed. There were no histologic changes of urethral and bladder mucosa; no histological changes in testes, thyroid gland, hypophysis, suprarenal glands, kidneys, liver, lungs, and heart were observed (Svystov 2003). In our study of topical tolerability in *Galleria* models (Osmanov, Wise and Denning 2019), the limit of tolerability for topical use at any concentration up to 32 000 mg/L was not achieved.

Insect models of efficacy

We have studied *in vivo* efficacy of miramistin using *Galleria* models. *G. mellonella* larvae were infected systemically with the LD_{90} of microorganism suspension. *G. mellonella* larvae received systemic injection of miramistin at 1, 6 and 24 hr post-infection. Dose range response experiments were performed using the concentrations of 16 mg/kg, 160 mg/kg and 1000 mg/kg.

Larvae were observed at 24 hr intervals for survival for 120 hr. Treatment failure was defined as death of a larva, while treatment success was defined as larva survival. We found that miramistin was protective against *C. albicans* at doses of 16 mg/kg and 160 mg/kg (Osmanov, Wise and Denning 2019). Miramistin was protective against *A. fumigatus* at 16 mg/kg.

Immunomodulatory properties

Miramistin also has immunomodulatory and immunoadjuvant properties (Vozianov *et al.* 1990). Increased phagocytosis was observed when miramistin was included in the treatment of chronic urethroprostatitis (Vozianov *et al.* 1990). When used for the treatment of purulent wounds miramistin increased the activity of neutrophil lactate dehydrogenase and reduced the activity of alpha-glycerol phosphate dehydrogenase and glucose-6-phosphate dehydrogenase (Gordienko 1999).

There are several clinical studies that demonstrate the immunomodulatory properties of miramistin, such as for the treatment of urethroprostatitis, oropharynx and the upper respiratory tract. These studies have shown that miramistin drives a dose dependent increase of phagocytosis of urethral neutrophil granulocytes with the maximum stimulatory effect being observed at a concentration of 0.001% (Shatrov, Krivoshein and Kovalenko 1990). Miramistin irrigation of palatal tonsillar lacunae in chronic tonsillitis maintained the optimal ratio of viable to apoptotic lymphocytes (Mukhomedzianova *et al.* 2011). Miramistin irrigation can also normalize the level of immunoglobulins in palatal tonsils by increasing the level of IgM and IgG yet decreasing the level of IgA (Mukhomedzianova *et al.* 2011).

Synthesis and biodegradation

We describe the synthesis of miramistin in Supplementary data.

Biodegradation is the process in which organic substances are being decomposed by microorganisms Natural microbial communities of soil and water are key players in this process and biodegradation is considered to be the most important process of eliminating pharmaceuticals (Yazdankhah *et al.* 2006). However, the knowledge of biodegradation of pharmaceuticals is scarce so far (Barra Caracciolo, Topp and Grenni 2015). Contamination of the environment by antiseptics is a growing concern due to their toxicity to microbiota, fish, algae and plants, and emerging cross-resistance with antibiotics (Barra Caracciolo, Topp and Grenni 2015). Antiseptics that have chlorinated aromatic structures, namely triclosan and triclocarban, are of the major concern due to their resistance to biodegradation; which means they can persist in the environment for significant periods, even for decades (Yazdankhah *et al.* 2006). The work by (Svystov 2003) [Свистов 2003] has shown that miramistin has biodegradability of 88–93%. These results are consistent with biodegradability data for other quaternary ammonium compounds which have biodegradability ranging from 83 to 93% with resulting products that do not have genotoxic effects (Grabińska-Sota 2011).

Clinical experience of using miramistin

All studies cited had full and appropriate ethical approval according to the local regulations of the country of origin. Miramistin was first clinically used in the early 1980s. Later, there were multiple clinical trials of miramistin. Miramistin has been used topically but never systemically. The same concentration of 0.01% was used in different studies and clinical scenarios.

Miramistin has been used for the management of active skin infections (Молочное *et al.* 2003) and wound infection management (Sytnik and Shidlovskiy 1993; Grigor'yan *et al.* 2014) [Сытник and Шидловский 1993; Григорьян *et al.* 2014]. Miramistin was also used in the management of burns (Loginov, Krivoshein and Shakhlamov 2002; Smirnov, Loginov and Shakhlamov 2002) [Логинов, Кривошеин and Шахламов 2002; Смирнов, Логинов and Шахламов 2002]. Eye drops with 0.01% solution of miramistin was used as an empiric treatment for mild eye infection as well as an adjunctive regimen for post-surgical antimicrobial prophylaxis (Ivanova, Bobrova and Krivoshein 1999; Maychuk, Selivorstova and Yakushina 2011) [Иванова, Боброва and Кривошеин 1999; Майчук, Селивёрстова and Якушина 2011].

Irrigation with miramistin solution was used for treatment of vulvovaginal candidiasis and other causes of vaginal discharge (Kirichenko 2013; Andreyeva and Levkovich 2016) [Кириченко 2013; Андреева and Левкович 2016]. There is also experience of postcoital prophylaxis of STDs in men and women (Milyavskiy *et al.* 1996; Rishchuk, Gusev and Dushenkova 2012) [Милявский *et al.* 1996; Рищук, Гусев and Душенкова 2012]. Miramistin was used as an adjunctive treatment for urogenital infection by applying miramistin solution into urethra (Nekhoroshikh *et al.* 2000, Gabidulina *et al.* 2002) [Нехороших *et al.* 2000; Габидулина *et al.* 2002]

In dentistry, clinical experience includes treatment of gingivitis (Kalantarov 2012) [Калантаров 2012] and use as a component of root canal fillings (Budzinskii and Syrac 2013; Samokhina *et al.* 2013) [Будзинский and Сирак 2013; Самохина *et al.* 2013]. There is clinical experience of irrigation with miramistin solution for treatment of nasopharyngitis and tonsillitis (Zavaliy 1997; Kustov 2015) [Завалий 1997; Кустов 2015]. In children, miramistin was used for irrigation of mucosa during rhinitis and tonsillitis (Kunel'skaya and Machulin 2013; Shabaldina, Ryazantsev and Shabaldin 2015; Kryukov *et al.* 2016) [Кунельская and Мачулин 2013; Шабалдина, Рязанцев and Шабалдин 2015; Крюков *et al.* 2016]. Nebulized miramistin solution (0.01%) was used as an adjunctive therapy for bronchitis (Khan *et al.* 2015) [Хан *et al.* 2015].

Despite the significant numbers of studies, the majority were small, not randomized, had poor or no microbiology follow-up which lead to a range of biases and possible data misinterpretations. There are only a few clinical trials that are randomized (Boyko, Kalinkina and Gorshkova 2012; Barlamov and Yesyunina 2014; Shabaldina, Ryazantsev and Shabaldin 2015) [Бойко, Калинкина and Горшкова 2012; Барламов and Есюнина 2014; Шабалдина, Рязанцев and Шабалдин 2015], all comparing miramistin with no treatment, rather than superiority or non-inferiority over other well-known compounds.

At the same time, the Russian registry of adverse drug reaction contains 15 references of adverse reactions to miramistin with one reaction leading to subcutaneous inflammation and others are allergic in nature (14 in total). Out of these 14 allergic reactions, three patients received other drugs concurrently that could potentially lead to allergic reactions. Hence, clinical experience of using miramistin is indicative of its good safety profile and tolerability.

SUMMARY OF MOST COMMONLY USED ANTISEPTICS AS COMPARATORS OF MIRAMISTIN

Chlorhexidine

Chlorhexidine is a divalent cationic biguanide biocide with a broad spectrum of antimicrobial activity. Currently, chlorhexidine is the mainstay antiseptic in the prevention of healthcare-associated infections. There are several formulations of chlorhexidine but the most commonly used is the water-soluble form, chlorhexidine gluconate (Silvestri and McEnery-Stonelake 2013). In addition, chlorhexidine may be impregnated into wound dressings and central line catheters. Chlorhexidine is increasingly used for bathing of patients and for universal decolonization. There is conflicting evidence regarding emerging resistance to chlorhexidine (Russell and Path 1986; Macias *et al.* 2016).

Chlorhexidine is a broad spectrum antiseptic that also shows long-lasting residual activity (Macias *et al.* 2016). It is most active against Gram-positive bacteria but also possesses activity against Gram-negative bacteria, fungi, and some enveloped viruses (Williamson, Carter and Howden 2017). Chlorhexidine is a positively charged molecule that binds to negatively charged microbial membranes and the cell wall. At lower concentrations, it leads to the loss of potassium ions and inhibition of cellular respiration; while at higher concentrations, chlorhexidine alters membrane integrity which results in a leakage of cellular content and eventual cell death (Russell and Path 1986).

Triclosan

Triclosan belongs to the bisphenol group of compounds and shows broad antimicrobial activity. Triclosan is used in numerous health and hygiene products, including surgical scrubs, soaps, clinical hand washes, mouthwashes and toothpastes (Jones *et al.* 2000). In the clinical setting triclosan was used mainly for MRSA decolonization but it was superseded by chlorhexidine due to its higher efficacy (Williamson, Carter and Howden 2017). Triclosan was incorporated into a range of plastics and fabrics including toothbrush handles, mop handles, children's toys, and surgical drapes. However, recent work has demonstrated lack of triclosan efficacy in household soap products leading to prohibition of triclosan and 18 other biocidal chemicals in consumer antiseptic products by the US Food and Drug Administration (FDA) (McNamara and Levy 2016). Cai *et al.* (2019) have found that triclosan concentrations in urine negatively correlate with bone marrow density and positively correlate with the prevalence of osteoporosis in US women. Triclosan is resistant to biodegradation which means that it can remain in the environment for substantial periods, even for decades (Yazdankhah *et al.* 2006). This makes contamination of the environment by triclosan of the major concern because of its toxicity to microbiota, plants and fish, and emerging cross-resistance with antibiotics (Barra Caracciolo, Topp and Grenni 2015).

Triclosan has broad antimicrobial activity against bacteria but also possesses some activity against viruses and fungi (Russell 2004). It was thought for many years that triclosan had a non-specific activity against cell membranes in a similar manner to other biocides (Gomez Escalada *et al.* 2005). However, recently there has been evidence to show that triclosan binds to the protein complex known as Fabl or InhA in *Mycobacterium spp.* (Heath et al. 1999a, 1999b; Prabhakaran, Abu-Hasan and Hendeles 2017). This results in the inhibition of fatty acid synthesis within microbial cells (Heath, White and Rock 2001).

Benzalkonium chloride

Benzalkonium chloride belongs to the group of quaternary ammonium compounds and has broad antimicrobial activity. Benzalkonium chloride is widely used in cosmetic products such as nose decongestant lotions, facial cleansers, acne treatment, moisturizers, hair conditioners, hair color and styling products, sun protection creams, baby lotions, eyewash/artificial tears, pain relief poultices or creams, cosmetics, cosmetic removal products and hand sanitizers. It is also used as a component of hand rubs, as a decontaminating agent of environment surfaces and healthcare devices (Buffet-Bataillon *et al.* 2012). Benzalkonium chloride is also used a topical antiseptic for wound dressing and mucosa, and in veterinary practice.

Benzalkonium chloride exhibits activity against Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, and it has a sporicidal activity. Benzalkonium chloride's long alkyl chain permeates the microbial membrane while the positively charged nitrogen remains on the outer surface. This causes alteration of the membrane and changes in charge distribution which leads to denaturation of the membrane protein. This leads to cytoplasmic leakage and eventual cell death. Additionally, benzalkonium chloride may bind to microbial DNA (Wessels and Ingmer 2013).

Decamethoxin (Decasan)

Decamethoxin is a broad-spectrum biocide that belongs to the group of bis-quaternary ammonium compounds. Decamethoxin is used for mucosal and skin infections, and in surgeries such as purulent and peritonitis surgery. It is also used for medical device disinfection and as an antiseptic in the prevention of health care-associated infections (Kravets 1987, 1991).

Decamethoxin is a broad-spectrum biocide that exhibits microbicidal activity against bacteria, fungi, and viruses. Decamethoxin accumulates in microbial cytoplasmatic membranes and binds to the phosphate groups of membrane lipids which leads to a decrease in permeability of the cytoplasmic membrane (Paliĭ, Kravets and Kvoal'chuk 1991; Lyapunov, Purtov and Dunay 2013) [Paliĭ, Kravets and Kvoal'chuk 1991; Ляпунов, Пуртов and Дунай 2013].

Dioxidine

Dioxidine is a broad-spectrum antiseptic that belongs to the group of quinoxaline derivatives. It is mainly used for treatment of purulent infections. Dioxidine is active against *Staphylococcus* spp. (including some MRSA strains), *Streptococcus* spp., *Meningococcus* spp., and Gram-negative bacteria. Dioxidine also exhibits antimicrobial activity against anaerobes including; *Clostridium* spp., *Bacteroides* spp. (including *B. fragilis*), *P. acnes*, *Lactobacterium* spp., *Bifidobacterium* spp., *Veillonella* spp., *Peptostreptococcus* spp., *P. niger*, as well as actinomycetes.

Dioxidine has microbicidal activity which is caused by inhibition of DNA synthesis and alteration of DNA integrity. Dioxidine activity increases in anaerobic environments due to the increased release of active oxygen from the dioxidine molecule (Torres-Viera *et al.* 2000a; Popov *et al.* 2013) [Torres-Viera *et al.* 2000a; Попов *et al.* 2013].

Taurolidine

Taurolidine is an antiseptic derived from the aminosulfoacid taurine. Taurolidine is mainly used as a catheter lock solution (O'Grady *et al.* 2011). The use of taurolidine for pleural decontamination during surgery for chronic pulmonary Aspergillosis and for peritonitis surgery has also been described (Caruso *et al.* 2010; Farid *et al.* 2013). Additionally, taurolidine has antineoplastic activity and has a potential role in cancer therapy (Jacobi, Menenakos and Braumann 2005).

Taurolidine is active against Gram-positive bacteria (including MRSA), Gram-negative bacteria, anaerobes and fungi (Torres-Viera *et al.* 2000b). The antimicrobial of action of taurolidine is caused by release of methylol taurinamide and taurine which results in alteration of the microbial cell wall, neutralization of the bacterial endotoxins, and intra- and inter-molecular cross-linking of the lipopolysaccharide-protein complex (Torres-Viera *et al.* 2000b).

N-chlorotaurine

N-chlorotaurine (NCT) is the derivative of the amino acid taurine and it is one of the oxidants produced by activated human granulocytes, monocytes, and macrophages (Malle et al. 2000a, 2000b). Clinical studies have shown good tolerability of NCT in the eye, in the paranasal sinuses, mucous membranes and on the skin (Lorenz et al. 2009a, 2009b; Gottardi and Nagl 2010). NCT has shown efficacy in chronic leg ulcers with purulent coating external otitis and bacterial and viral conjunctivitis (Nagl *et al.*

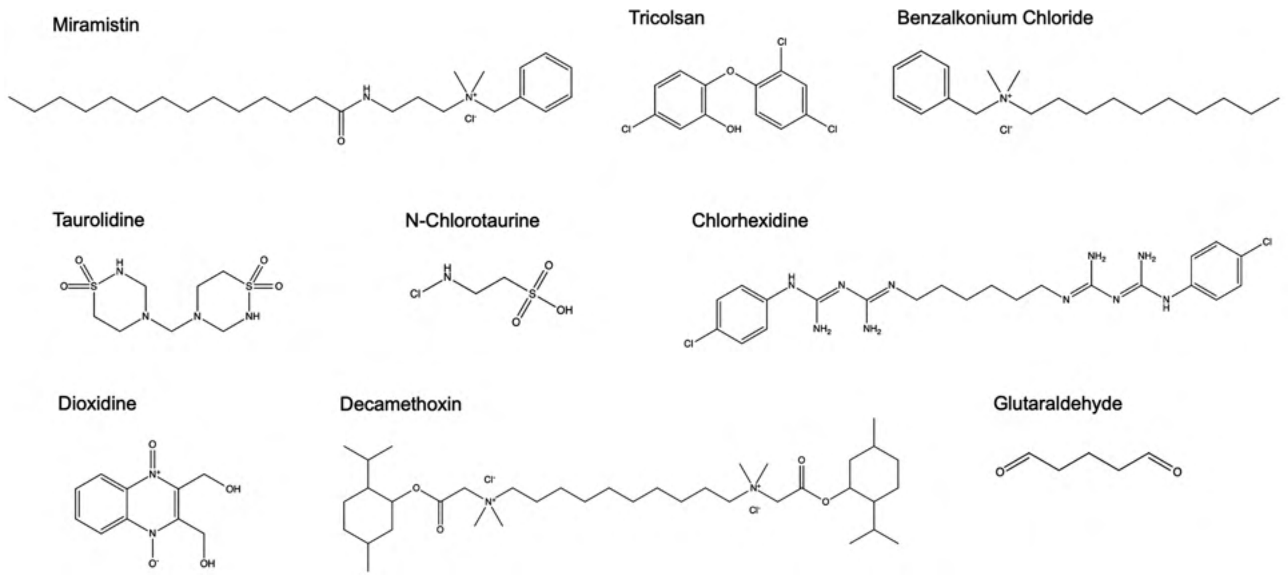

Figure 3. Structures of antiseptics.

2000; Neher *et al.* 2004; Lorenz *et al.* 2009b; Gottardi, Debabov and Nagl 2013). Inhalation of this antiseptic has been used to treat respiratory infection, including fungal infections. Studies on mice (Nagl *et al.* 2013), pigs (Geiger *et al.* 2009; Schwienbacher *et al.* 2011) and a phase I clinical trial (Nagl, Arnitz and Lackner 2018) was used to show tolerability of NCT for this purpose.

NCT has broad antimicrobial activity against bacteria, viruses, parasites, and fungi (Lorenz *et al.* 2009b; Gottardi and Nagl 2010). Antimicrobial activity of NCT against bacteria and fungi is caused by chlorine transfer from NCT to low molecular weight amino compounds, generally to ammonium chloride but also to some amino acids. The formation of ammonium chloride results in production of stronger microbicidal monochloramine and as a result, antimicrobial activity of NCT is enhanced (Nagl *et al.* 2001; Gottardi and Nagl 2005a). Additionally, NCT causes surface chlorination of pathogens that leads to lack of microorganism growth and decrease of virulence (Nagl *et al.* 1999; Gottardi and Nagl 2005b; Eitzinger *et al.* 2012). It was shown that NCT induces oxidative stress response and inhibits mycelial growth in *A. fumigatus* (Sheehan, Nagl and Kavanagh 2019). NCT also has activity against bacterial biofilms (Ammann *et al.* 2014; Coraça-Huber *et al.* 2014). Moreover, NCT has anti-inflammatory activity caused by down-regulation of production of pro-inflammatory mediators (Schuller-Levis and Park 2003; Gottardi and Nagl 2010).

Glutaraldehyde

Glutaraldehyde is a saturated dialdehyde that has gained wide acceptance as a disinfectant and chemical sterilant. Since its introduction in the early 1960 s, it has been used extensively for disinfection and sterilization in health services. Glutaraldehyde is used in a variety of ways (Gorman, Scott and Russell 1980; Kampf 2018). In addition to its use as a biocide (most commonly in disinfectants). In health settings glutaraldehyde is used in endoscopy units, operating theatres; X-ray film processing; dental units and ear nose and throat departments. Aqueous solutions of glutaraldehyde are acidic and generally in this state are not sporicidal. Only when the solution is 'activated' (made alkaline) by use of alkalinating agents to pH 7.5–8.5 does the solution become sporicidal. Once activated, these solutions have a shelf life of minimally 14 days. Like formaldehyde, the biocidal activity of glutaraldehyde results from its alkylation of sulfhydryl, hydroxyl, carboxyl, and amino groups of microorganisms, which alters RNA, DNA, and protein synthesis.

The application of alkaline glutaraldehyde in healthcare and commercial settings is supported by an exhaustive literature (reviewed in (Gorman, Scott and Russell 1980). It has a broad spectrum of activity and a rapid rate of killing and after many years of use has earned a justified reputation as an efficient disinfectant. Vegetative bacteria are readily susceptible to the action of glutaraldehyde. A 0.02% aqueous alkaline solution is rapidly effective against Gram positive and Gram negative species, whilst a 2% solution is capable of killing many vegetative species, including *Staphylococcus aureus*, *Proteus vulgaris*, *Escherichia coli* and *Pseudomonas aeruginosa* within 2 min (reviewed in (Gorman, Scott and Russell 1980). Sehmi *et al.* (2016) prepared novel materials in which glutaraldehyde was incorporated into polyurethane. While a 99.9% reduction in the numbers of *S. aureus* and *E. coli* occurred within 1–2 hours only, this faded after 15 days.

At the use-dilution of 2%, glutaraldehyde is capable rapidly killing *Bacillus* and *Clostridium* spp. spores (reviewed in (Gorman, Scott and Russell 1980). Rubbo and collagues reported a 99.99% kill of spores of *B. anthracis* and *C. tetani* in 15 and 30 min respectively (Rubbo, Gardner and Webb 1967). But not all species are equally susceptible. *B. subtilis* spores appear to be the most resistant to treatment with glutaraldehyde; 10 hours was necessary for complete kill, but 3 h contact period gave approximately a six log drop in viable count (Miner *et al.* 1977).

Glutaraldehyde (1% and 2% solutions) is active against of dermatophytes and *Candida* spp. In early studies, *Aspergillus niger* was more resistant than other fungi to glutaraldehyde ((Rubbo, Gardner and Webb 1967; Gorman, Scott and Russle 1980). More recent work has shown that glutaraldehyde in solution, caused a 10^4 or more reduction in viability of *A. fumigatus* strains in less than 5 min contact time. Many studies have confirmed the virucidal activity of glutaraldehyde even in the presence of high levels of organic matter (reviewed in (Gorman, Scott and Russle 1980)). One important proviso is that papovaviruses and parvoviruses might be somewhat resistant to chemical inactivation.

Table 4. Comparison of most commonly used antiseptics.

Antiseptic	Class	Mode of Action	Antimicrobial spectrum	Clinical use	Comments
Miramistin	Quaternary ammonium compound	Penetration of the bacterial membrane with altering charge distribution and consequent disruption of the membrane. Solubilization of the membrane and higher concentrations and direct binding to microbial DNA.	Broad activity against bacteria, viruses, and fungi.	Wound and burn management Rhinitis, sinusitis and tonsillitis Otitis externa Conjunctivitis Vaginitis Postcoital prevention of STDs	Resistance is uncommon Activity against resistant fungal strains
Chlorhexidine	Divalent cationic biguanide	Targets microbial membranes and the cell wall. Leads to the loss of potassium ions and inhibition of cellular respiration at lower concentrations, alters membrane integrity at higher concentrations	Most active against Gram-positive, also against Gram-negative, fungi, and some enveloped viruses	Skin and mucosa decontamination and disinfection Wound management Component of mouthwashes	Widely used to prevent healthcare-associated infections Mixed evidence on resistance
Triclosan	Bisphenol	Binds to the protein complex FabI or InhA resulting in the inhibition of fatty acid synthesis	Broad activity against bacteria, also possesses some activity against viruses and fungi	Disinfectant or preservative in consumer products Impregnation of medical devices	Resistance is common. Evidence of cross-resistance with antibiotics. Concerns over triclosan being linked to osteoporosis in women. Prohibited by FDA in consumer antiseptic products. Contamination of the environment by triclosan is of the major concern.
Benzalkonium chloride	Quaternary ammonium compound	Alteration of the membrane and changes in charge distribution which leads to denaturation of membrane proteins leading to cytoplasmic leakage	Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, and a sporicidal activity	Skin disinfection Wound management Preservative in pharmaceutical products including such as eye, ear and nasal drops	

Table 4. Continued

Antiseptic	Class	Mode of Action	Antimicrobial spectrum	Clinical use	Comments
Decamethoxin (Decasan)	Bis-quaternary ammonium compound	Accumulates in microbial cytoplasmatic membranes and binds to the phosphate groups of membrane lipids leading to a decrease in permeability of the cytoplasmic membrane	Broad-spectrum microbicidal activity against bacteria, fungi, and viruses	Skin decontamination and disinfection Irrigation of peritoneal cavity during surgery Disinfection of medical devices	
Dioxidine	Quinoxaline derivatives	Inhibition of DNA synthesis and alteration of DNA integrity	Broad antibacterial activity including anaerobes	Wound management	Concerns over dioxidine inducing cross-resistance with antibiotics
Taurolidine	Aminosulfoacid taurine derivative	Release of methylol taurinamide and taurine which resulting in alteration of the cell wall, neutralization of the bacterial endotoxins, and molecular cross-linking of the lipopolysaccharide-protein complex	Gram-positive bacteria, Gram-negative bacteria, anaerobes and fungi	Pleural and peritoneal decontamination during surgery Impregnation of catheters	
N-chlorotaurine (NCT)	Taurine derivative	Chlorine transfer from NCT to low molecular weight amino compounds, generally to ammonium chloride but also to some amino acids; surface chlorination of pathogens; induction of oxidative stress response	Broad activity against bacteria, viruses, parasites, and fungi	Wound management Otitis externa Conjunctivitis Rhinitis and sinusitis Nebulization for chronic pulmonary fungal infections	Has anti-inflammatory properties
Glutaraldehyde	Saturated dialdehyde	Number of mechanisms proposed to explain biocidal properties Like many other aldehydes, it reacts with amines and thiol groups, which are common functional groups in proteins. Being bi-function, it is also a potential crosslinker, resulting in cell death	Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, and sporicidal activity	Broad range of healthcare settings, systems disinfection	Resistance is uncommon Activity against resistant fungal strains

Table 5. Possible clinical and hospital use of an antiseptic miramistin.

Possible indication	Current practice(s)	Clinical experience of using miramistin for this purpose (references)	Comments on using miramistin for this purpose
Wounds, particularly fungal and mixed infection wounds	Systemic antibiotics and antifungals Surgical debridement Adjunctive therapy with topical antiseptics	Yes (Sytnik and Shidlovskiy 1993; Molonchnoye *et al.* 2003; Grigor'yan *et al.* 2014) [Сытник and Шидловский 1993; Молочное *et al.* 2003; Григорьян *et al.* 2014]	Broad antimicrobial activity Potent antifungal activity May reduce use of systemic antifungal agents Good safety profile May be useful for microorganisms that are resistant to other antiseptics, triclosan and chlorhexidine in particular
Diabetic foot ulcers		Yes (Kurdekbaev 2013) [Курдекбаев 2013]	
Chronic wounds		Yes (Blatun 2011) [Блатун 2011]	
Burns management	Surgical debridement Systemic antibiotics Topical antibiotics Antiseptics	Yes (Loginov, Krivoshein and Shakhlamov 2002; Smirnov, Loginov and Shakhlamov 2002) [Логинов, Кривошеин and Шахламов 2002; Смирнов, Логинов and Шахламов 2002]	
Prevention of upper respiratory tract infections	Cetylpyridinium chloride	No	
Oral mucosal infections, notably candidiasis	Chlorhexidine Triclosan	Yes (Kalantarov 2012; Kunel'skaya and Machulin 2013; Fleysher 2015; Shabaldina, Ryazantsev and Shabaldin 2015; Kryukov *et al.* 2016) [Калантаров 2012; Кунельская and Мачулин 2013; Флейшер 2015; Шабалдина, Рязанцев and Шабалдин 2015; Крюков *et al.* 2016]	
Otitis externa	Non-antibiotic (antiseptic or acidifying), non-ototoxic drops topical preparations, Antibiotic drops	Yes (Kaygorodtsev and Korkmazov 2012) [Кайгородцев and Коркмазов 2012]	
Fungal keratitis	Systemic antifungals Topical antifungals	No	
Conjunctivitis (empiric treatment), antimicrobial prophylactics in eye injuries	Systemic antimicrobials Topical antimicrobials and antiseptics	Yes (Ivanova, Bobrova and Krivoshein 1999; Maychuk, Selivorstova and Yakushina 2011) [Иванова, Боброва and Кривошеин 1999; Майчук, Селивёрстова and Якушина 2011]	
Vulvovaginal candidiasis/recurrent vulvovaginal candidiasis (rVVC)	Antiseptics locally Systemic antifungals Azole resistant *Candida glabrata* an increasing problem	No but was used for other causes of vaginal discharge (Kirichenko 2013; Andreyeva and Levkovich 2016) [Кириченко 2013; Андреева and Левкович 2016]	
Intra-abdominal surgical wash	Various antiseptics	Yes (Shpilevoy, Segalov and Filatov 1993; Gordiyenko and Filatov 1997) (Шпилевой, Сегалов and Филатов 1993; Гордиенко and Филатов 1997)	
Chronic ambulatory peritoneal dialysis-related peritonitis	Antibiotic instillation and systemic antibiotics or antifungals	Yes, in one patient (Krutikov *et al.* 2004) [Крутиков *et al.* 2004]	
Hand/skin decontamination	Various antiseptics, mainly chlorhexidine	No	
Nasal decontamination for prevention of surgical site infection	Chlorhexidine	No	

Table 5. Continued

Possible indication	Current practice(s)	Clinical experience of using miramistin for this purpose (references)	Comments on using miramistin for this purpose
Animal and human bites	Surgical debridement Irrigation with antiseptics Systemic antimicrobial prophylaxis depending on the risk group and a source of a bite (e.g. dog, bat, or human) Rabies and tetanus vaccination may be necessary	No	
Postcoital prophylaxis of STDs	Empiric antimicrobial prophylaxis for chlamydia, gonorrhoea, and trichomonas Individualized HIV PEP HPV vaccination Postexposure HBV vaccination	Yes (Milyavskiy *et al.* 1996; Rishchuk, Gusev and Dushenkova 2012) [Милявский *et al.* 1996; Рищук, Гусев and Душенкова 2012]	
Superficial infections with non-dermatophyte moulds	Topical antifungals, although resistance to terbinafine is emerging	No	Active against non-dermatophyte moulds
Nebulized solution for fungal asthma (ABPA and SAFS) and *Aspergillus* tracheobronchitis or antifungal prophylaxis	Antifungals, especially amphotericin B	Not for this purpose, but it was used as a nebulized solution (Хан *et al.* 2015)	May potentially lead to bronchospasm in some patients
Inclusion into root canal fillings/irrigation	Calcium hydrochloride/chlorhexidine as component of filling Natrium hypochlorite, alcohol, or chlorhexidine for irrigation	Yes (Samokhina *et al.* 2013; Budzinskii and Syrac 2013) [Самохина *et al.* 2013; Будзинский and Сирак 2013]	High concentration may be used for this purpose
Impregnation onto catheters/medical devices	Impregnation with antiseptics, particularly chlorhexidine	Yes (Budzinskii and Syrac 2013) [Будзинский and Сирак 2013]	
Impregnation onto surgical sutures	Coating with triclosan	Yes (Krutyakov *et al.* 2016)	
Impregnation onto silver nanoparticles	Use of silver nanoparticle impregnated with antiseptics is to mitigate an antimicrobial resistance is an emerging research topic. Various antiseptics/combinations of antiseptics are used (benzalkonium chloride, quaternary ammonium compounds, Virkon®S, chlorehedine, hydrogen peroxide and sodium hypochlorite) (Lu *et al.* 2017; Mohammed and Abdel Aziz 2019)	Pre-cinical experience (Krutyakov *et al.* 2016)	
Incorporation into anti-microbial fabrics	Silver nanoparticles without antiseptics; Silver nanoparticles impregnated with antiseptics, mainly QACs	No	
Medical device decontamination	Various antiseptics, mainly chlorhexidine Hydrogen peroxide	Yes (Devdera, Nidzel's'kyy and Tserbrzhyns'kyy 2008) [Девдера, Нiдзельський and Цебржинський 2008]	
Surface decontamination	Various compounds including Virusolve, Vircon, quaternary ammonium compounds, and benzalkonium chloride	Yes	

ABPA = allergic bronchopulmonary aspergillosis, SAFS = severe asthma with fungal sensitisation.

Chemical properties and patent data for these antiseptics are summarized in Table 3, antiseptics are compared in Table 4, and the chemical structures of these antiseptics are presented in Fig. 3.

DISCUSSION

In light of increasing antimicrobial resistance, the role and appropriate use of antiseptics has become more important as they may act as a 'last frontier' to prevent outbreaks of multi-resistant organisms (Daneman *et al.* 2013), shown by the experience with *C. auris* (Abdolrasouli *et al.* 2017; Jeffery-Smith *et al.* 2018).

Current antiseptic products belong to a number of different chemical classes. Antiseptics with broad spectrum antimicrobial action usually exhibit lesser activity against fungal species compared to bacterial. Also, using an antiseptic is a compromise between their antimicrobial activity and safety (Hirsch *et al.* 2010).

There is emerging evidence of resistance to antiseptics, documented in particular for teampulin, chlorhexidine, triclosan, and benzalkonium chloride (Williamson, Carter and Howden 2017). There are two major categories of resistance to antiseptics: intrinsic and acquired. Intrinsic non-susceptibility is mediated via impermeability of the cell wall, biofilm and spore formation and enzymatic degradation (Sheldon 2005; Bonez *et al.* 2013). Acquired resistance is caused by overexpression of a target for antiseptic of efflux pumps, mutation of a target site and activation of enzymes (Poole 2005; Sheldon 2005). There are two worrisome trends in antiseptics resistance. The first trend is cross resistance with antibiotics. Benzalkonium chloride cross-resistance with antibiotics sulfamethoxazole, ampicillin, and cefotaxime is one example (Kampf 2018). Another example is chlorhexidine cross-resistance with sulfamethoxazole, ceftazidime, tetracycline, cefotaxime, and imipenem (Braoudaki and Hilton 2004; Pumbwe, Skilbeck and Wexler 2007; Knapp *et al.* 2013; Wand *et al.* 2017). Cross-resistance to sulfamethoxazole, cefotaxime, ceftazidime, and chloramphenicol sulfamethoxazole, cefotaxime, ceftazidime, chloramphenicol was also found with octenidine, didecyldimethylammonium chloride, sodium hypochlorite, and triclosan (Kampf 2018). The second trend is emerging resistance to antiseptics among MRSA (Hughes and Ferguson 2017; Williamson, Carter and Howden 2017) and decreased susceptibility of *C. auris* biofilms (Kean *et al.* 2018).

A new compound with a new mechanism of action may be effective in the prevention of emerging resistance to antiseptics (Butler, Blaskovich and Cooper 2013). Miramistin is a potential candidate for this purpose as its mode of action differs from well-known antifungal agents and most antiseptics (Fredell 1994; Кривошеин 2004; Gilbert and Moore 2005; Theuretzbacher *et al.* 2015). Due to the substantial differences in the way cationic antiseptics interact with a microbial cell wall, resistance to one cationic agent does not lead to development of resistance to another cationic antiseptic (Gilbert and Moore 2005). This is consistent with global stewardship efforts for antimicrobial use that aim for the reduction of resistance emerging (Brotherton 2018; Cunha 2018a, 2018b).

Possible uses of miramistin

Possible indications for miramistin are summarized in the Table 5. These are primarily topical uses. Additional specific safety studies would need to be conducted for some uses, such as ocular administration and nebulization. Medical equipment decontamination usage would require additional data on its impact on that equipment, if used repeatedly.

Further clinical studies

Among proposed possible indications we surmise that the most promising is the use of miramistin for treatment of acute and chronic wounds and skin infections. Due to the poor design of previously performed clinical trials, it is essential to perform properly designed clinical trials to evaluate the efficacy of miramistin for this purpose. Given the previous clinical experience being indicative of a good safety profile, phase III non-inferiority trials comparing the clinical efficacy of miramistin in this indication would be helpful. These trials should address two points: i) non-inferiority of miramistin over currently used best practices; ii) achieved reduction in the use of systemic antimicrobials.

CONCLUSION

Previous research indicates that miramistin has a broad antimicrobial spectrum; however, highly reproducible methodologies were not utilized in these studies. Nevertheless, the available information suggests broad antimicrobial activity and current clinical experience is also indicative of a good safety profile and tolerability of the compound. These data support the use of miramistin as a topical antiseptic, however, further research is needed.

SUPPLEMENTARY DATA

Supplementary data are available at *FEMSRE* online.

ETHICAL APPROVAL

Ethical approval is not required.

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Declaration of Interests. Dr Osmanov does not declare any conflicts of interest related to this work. Ms Farooq does not declare any conflicts of interest related to this work. Dr Richardson does not declare any conflicts of interest related to this work. Dr Denning and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Scynexis, Pulmatrix, Pulmocide, Zambon, iCo Therapeutics, Mayne Pharma, Roivant and Fujifilm. In the last 3 years, he has been paid for talks on behalf of Gilead, Merck, Mylan and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee.

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