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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.

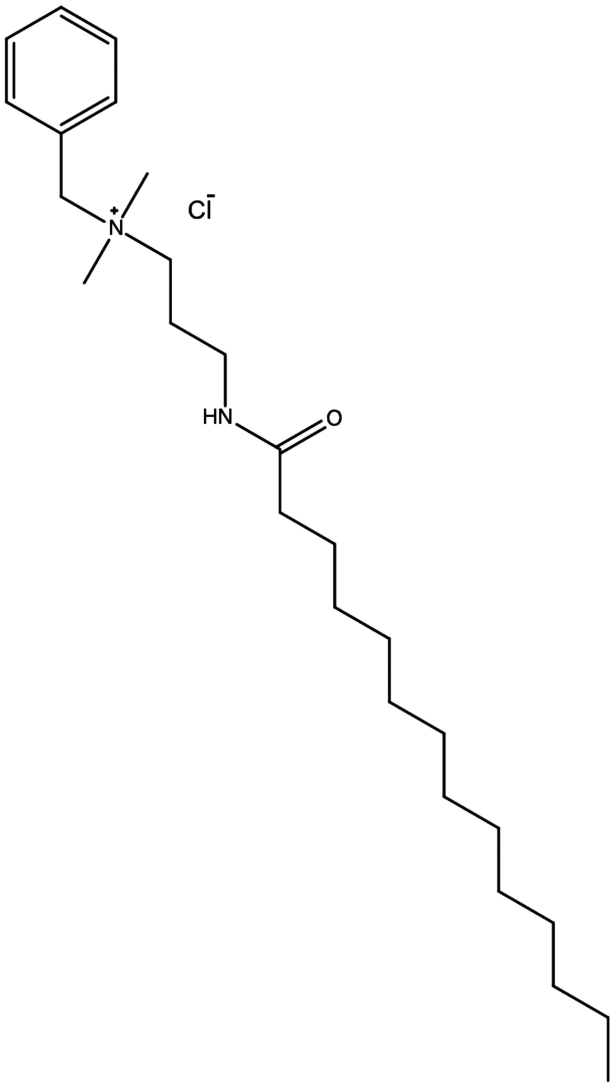

Figure 1. Miramistin molecule.

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

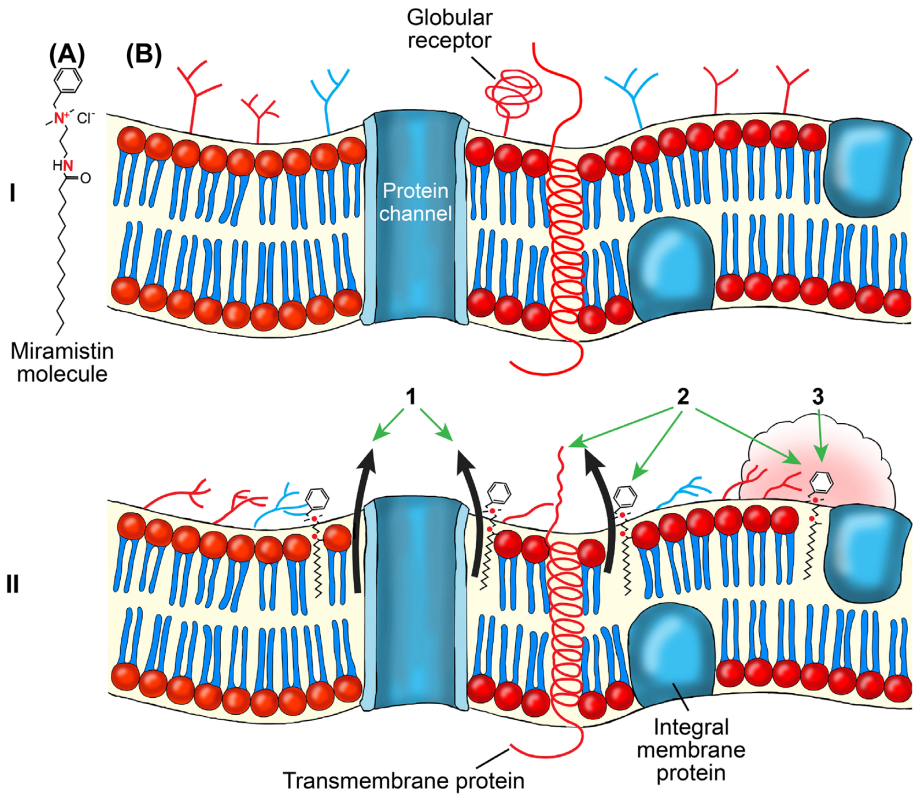

Figure 2. Mode of action of miramistin. (I) miramistin and normal membrane. **(A)** miramistin molecule and charge distribution (miramistin molecule is not in scale); **(B)** normal cellular membrane structure. (II) Interaction of miramistin with cellular membrane (miramistin molecule is approximately 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).

Strains	Miramistin		Fluconazole		Itraconazole	
	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 FabI 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 (Palíĭ, Kravets and Kvoal'chuk 1991; Lyapunov, Purtov and Dunay 2013) [Palíĭ, 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.*

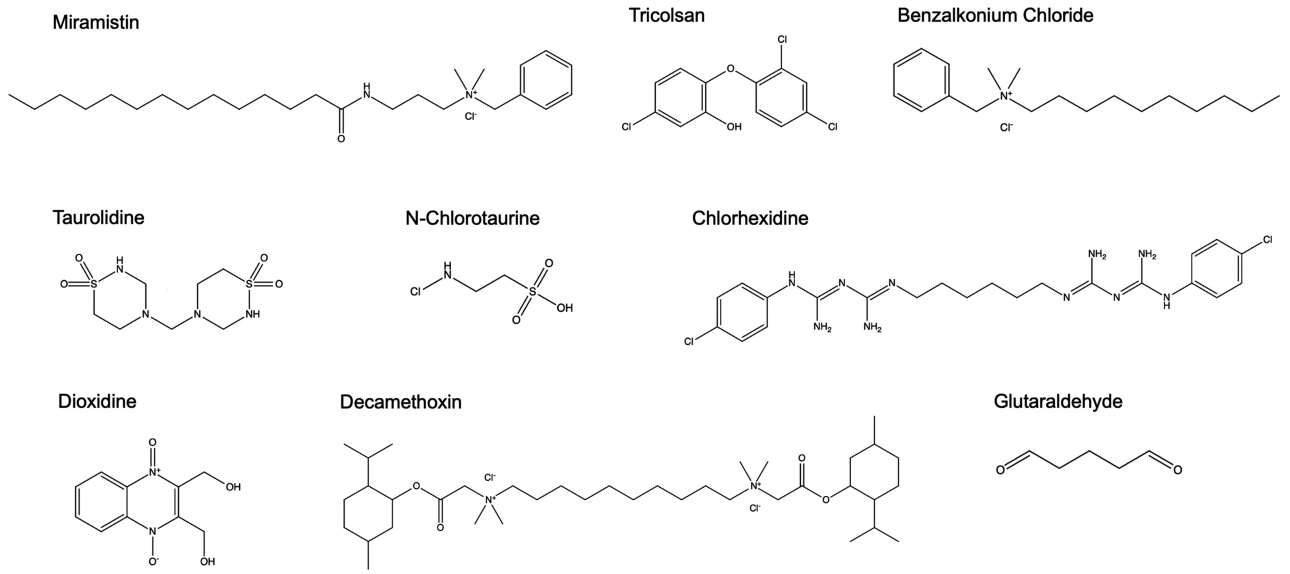

Figure 3. Structures of antiseptics.

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, Нідзельський 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.

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ETHICAL APPROVAL

Ethical approval is not required.

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.

REFERENCES

Abdolrasouli A, Armstrong-James D, Ryan L *et al*. In vitro efficacy of disinfectants utilised for skin decolonisation and environmental decontamination during a hospital outbreak with Candida auris. *Mycoses* 2017;**60**:758–63.

Ammann CG, Fille M, Hausdorfer J *et al*. Influence of poly-N-acetylglucosamine in the extracellular matrix on N-chlorotaurine mediated killing of Staphylococcus epidermidis. *New Microbiol* 2014;**37**:383–6.

Arzumanian VG. [Minimum inhibitory concentrations of various antifungal agents against Basidiomycetes clinical isolates]. *Antibiot i khimioterapiia = Antibiot chemoterapy [sic] / Minist meditsinskoĭ i Mikrobiol promyshlennosti SSSR* 2002;**47**:7–10.

Barra Caracciolo A, Topp E, Grenni P. Pharmaceuticals in the environment: Biodegradation and effects on natural microbial communities. A review. *J Pharm Biomed Anal* 2015;**106**:25–36.

Biswal M, Rudramurthy SM, Jain N *et al*. Controlling a possible outbreak of Candida auris infection: lessons learnt from multiple interventions. *J Hosp Infect* 2017;**97**:363–70.

Bonez PC, Dos Santos Alves CF, Dalmolin TV *et al*. Chlorhexidine activity against bacterial biofilms. *Am J Infect Control* 2013;**41**:e119–22.

Bragg R, Jansen A, Coetzee M *et al*. Bacterial resistance to Quaternary Ammonium Compounds (QAC) disinfectants. *Adv Exp Med Biol* 2014;**808**:1–13.

Bragg RR, Meyburgh CM, Lee J-Y *et al*. Potential Treatment Options in a Post-antibiotic Era. *Adv Exp Med Biol* 2018;**1052**:51–61.

Braoudaki M, Hilton AC. Adaptive resistance to biocides in Salmonella enterica and Escherichia coli O157 and cross-resistance to antimicrobial agents. *J Clin Microbiol* 2004;**42**:73–8.

Brotherton AL. Metrics of Antimicrobial Stewardship Programs. *Med Clin North Am* 2018;**102**:965–76.

Buffet-Bataillon S, Tattevin P, Bonnaure-Mallet M *et al*. Emergence of resistance to antibacterial agents: the role of quaternary ammonium compounds–a critical review. *Int J Antimicrob Agents* 2012;**39**:381–9.

Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. *J Antibiot (Tokyo)* 2013;**66**:571–91.

Cai S, Zhu J, Sun L *et al*. Association Between Urinary Triclosan With Bone Mass Density and Osteoporosis in US Adult Women, 2005–2010. *J Clin Endocrinol Metab* 2019;**104**:4531–8.

Caruso F, Darnowski JW, Opazo C *et al*. Taurolidine antiadhesive properties on interaction with E. coli; Its transformation in biological environment and interaction with bacteria cell wall. Hoheisel J (ed.). *PLoS One* 2010;**5**:e8927.

Ceragioli M, Mols M, Moezelaar R *et al*. Comparative transcriptomic and phenotypic analysis of the responses of Bacillus cereus to various disinfectant treatments. *Appl Environ Microbiol* 2010;**76**:3352–60.

Coraça-Huber DC, Ammann CG, Fille M *et al*. Bactericidal activity of N-chlorotaurine against biofilm-forming bacteria grown on metal disks. *Antimicrob Agents Chemother* 2014;**58**:2235–9.

Cunha CB. Antimicrobial Stewardship Programs. *Med Clin North Am* 2018a;**102**:797–803.

Cunha CB. The Pharmacoeconomic Aspects of Antibiotic Stewardship Programs. *Med Clin North Am* 2018b;**102**:937–46.

Daneman N, Sarwar S, Fowler RA *et al*. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;**13**:328–41.

Deutsches Institut fur Normung. DIN EN 1275: Chemical Disinfectants and Antiseptics – Quantitative Suspension Test for the Evaluation of Basic Fungicidal or Basic Yeasticidal Activity of Chemical Disinfectants and Antiseptics. *Berlin: Beuth* 2005.

Dumas O, Wiley AS, Henneberger PK *et al*. Determinants of disinfectant use among nurses in U.S. healthcare facilities. *Am J Ind Med* 2017;**60**:131–40.

Eitzinger C, Ehrlenbach S, Lindner H *et al*. N-chlorotaurine, a long-lived oxidant produced by human leukocytes, inactivates Shiga toxin of enterohemorrhagic Escherichia coli. *PLoS One* 2012;**7**:e47105.

Farid S, Mohamed S, Devbhandari M *et al*. Results of surgery for chronic pulmonary Aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence - a National Centre's experience. *J Cardiothorac Surg* 2013;**8**:1.

Fredell D. *Biological Properties and Applications of Cationic Surfactants*. MARCEL DEKKER AG, 1994.

Friedrich CL, Moyles D, Beveridge TJ *et al*. Antibacterial action of structurally diverse cationic peptides on gram-positive bacteria. *Antimicrob Agents Chemother* 2000;**44**:2086–92.

Fromm-Dornieden C, Rembe J-D, Schäfer N *et al*. Cetylpyridinium chloride and miramistin as antiseptic substances in chronic wound management - prospects and limitations. *J Med Microbiol* 2015;**64**:407–14.

Geiger R, Treml B, Pinna A *et al*. Tolerability of inhaled N-chlorotaurine in the pig model. *BMC Pulm Med* 2009;**9**:33.

Gilbert P, Al-taae A. Antimicrobial activity of some alkyltrimethylammonium bromides. *Lett Appl Microbiol* 1985;**1**:101–4.

Gilbert P, Moore LE. Cationic antiseptics: diversity of action under a common epithet. *J Appl Microbiol* 2005;**99**:703–15.

Gomez Escalada M, Russell AD, Maillard JY *et al*. Triclosan-bacteria interactions: Single or multiple target sites? *Lett Appl Microbiol* 2005;**41**:476–81.

Gordienko AI. [The influence of laser and electrophoresis of myramistin on dehydrogenases activity of the blood neutrophils in complex treatment of purulent complications in abdominal surgery]. *Klin Khir* 1999:25.

Gorman SP, Scott EM, Russle AD. Antimicrobial Activity, Uses and Mechanism of Action of Glutaraldehyde. *J Appl Bacteriol* 1980;**48**:161–90.

Gottardi W, Debabov D, Nagl M. N-chloramines, a promising class of well-tolerated topical anti-infectives. *Antimicrob Agents Chemother* 2013;**57**:1107–14.

Gottardi W, Nagl M. Chlorine covers on living bacteria: the initial step in antimicrobial action of active chlorine compounds. *J Antimicrob Chemother* 2005a;**55**:475–82.

Gottardi W, Nagl M. Chlorine covers on living bacteria: The initial step in antimicrobial action of active chlorine compounds. *J Antimicrob Chemother* 2005b;**55**:475–82.

Gottardi W, Nagl M. N-chlorotaurine, a natural antiseptic with outstanding tolerability. *J Antimicrob Chemother* 2010;**65**:399–409.

Grabińska-Sota E. Genotoxicity and biodegradation of quaternary ammonium salts in aquatic environments. *J Hazard Mater* 2011;**195**:182–7.

Group WS. *Evaluation and testing of drugs for mutagenicity: principles and problems, report of a WHO scientific group, 1971 protocol*'. 1971: Series No 482p. 68.

Harbarth S, Tuan Soh S, Horner C *et al*. Is reduced susceptibility to disinfectants and antiseptics a risk in healthcare settings? A point/counterpoint review. *J Hosp Infect* 2014;**87**:194–202.

Heath RJ, Rubin JR, Holland DR *et al*. Mechanism of triclosan inhibition of bacterial fatty acid synthesis. *J Biol Chem* 1999a;**274**:11110–4.

Heath RJ, Rubin JR, Holland DR *et al*. Mechanism of triclosan inhibition of bacterial fatty acid synthesis. *J Biol Chem* 1999b;**274**:11110–4.

Heath RJ, White SW, Rock CO. Lipid biosynthesis as a target for antibacterial agents. *Prog Lipid Res* 2001;**40**:467–97.

Hirsch T, Koerber A, Jacobsen F *et al*. Evaluation of toxic side effects of clinically used skin antiseptics in vitro. *J Surg Res* 2010;**164**:344–50.

Huang H, Chen B, Wang H-Y *et al*. The efficacy of daily chlorhexidine bathing for preventing healthcare-associated infections in adult intensive care units. *Korean J Intern Med* 2016;**31**:1159–70.

Hughes C, Ferguson J. Phenotypic chlorhexidine and triclosan susceptibility in clinical Staphylococcus aureus isolates in Australia. *Pathology* 2017;**49**:633–7.

Ioannou CJ, Hanlon GW, Denyer SP. Action of disinfectant quaternary ammonium compounds against Staphylococcus aureus. *Antimicrob Agents Chemother* 2007;**51**:296–306.

Jacobi CA, Menenakos C, Braumann C. Taurolidine–a new drug with anti-tumor and anti-angiogenic effects. *Anticancer Drugs* 2005;**16**:917–21.

Jeffery-Smith A, Taori SK, Schelenz S *et al*. Candida auris: a Review of the Literature. *Clin Microbiol Rev* 2018;**31**:e00029–17.

Jones RD, Jampani HB, Newman JL *et al*. Triclosan: A review of effectiveness and safety in health care settings. *Am J Infect Control* 2000;**28**:184–96.

Kampf G, Todt D, Pfaender S *et al*. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect* 2020;**104**:246–51.

Kampf G. Biocidal Agents Used for Disinfection Can Enhance Antibiotic Resistance in Gram-Negative Species. *Antibiotics* 2018;**7**:110.

Kean R, McKloud E, Townsend EM *et al*. The comparative efficacy of antiseptics against Candida auris biofilms. *Int J Antimicrob Agents* 2018;**52**:673–7.

Knapp L, Rushton L, Stapleton H *et al*. The effect of cationic microbicide exposure against *Burkholderia cepacia* complex (Bcc); the use of *Burkholderia lata* strain 383 as a model bacterium. *J Appl Microbiol* 2013;**115**:1117–26.

Koburger T, Hübner N-O, Braun M *et al*. Standardized comparison of antiseptic efficacy of triclosan, PVP-iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. *J Antimicrob Chemother* 2010;**65**:1712–9.

Kravets VP. [Complex treatment of acute purulent-inflammatory diseases of the fingers and hand using decamethoxine]. *Klin Khir* 1991:34–7.

Kravets VP. [Use of dekametoksin in treating acute suppurative inflammatory diseases of the hand]. *Vrach Delo* 1987:113–5.

Krivoshein YuS, Achkasova YuN, Bryzgunova NI *et al*. Effect of detergents on pathogenicity plasmids of escherichias. *J Hyg Epidemiol Microbiol Immunol* 1988;**32**:345–52.

Krutyakov Y, Klimov A, Violin B *et al*. Benzyldimethyl[3-(miristoylamino)-propyl]ammonium chloride stabilized silver nanoparticles (Argumistin™) in medicine: results of clinical trials for treatment of infectious diseases of dogs and perspectives for humans. *Eur J Nanomedicine* 2016;**8**:185–94.

Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J Infect Dis* 2017;**215**:S28–36.

Lorenz K, Mayer D, Bruhn G *et al*. Effect of N-chlorotaurine mouth rinses on plaque regrowth and plaque vitality. *Clin Oral Investig* 2009a;**13**:9–14.

Lorenz K, Mayer D, Bruhn G *et al*. Effect of N-chlorotaurine mouth rinses on plaque regrowth and plaque vitality. *Clin Oral Investig* 2009b;**13**:9–14.

Lowe CF, Lloyd-Smith E, Sidhu B *et al*. Reduction in hospital-associated methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus with daily chlorhexidine gluconate bathing for medical inpatients. *Am J Infect Control* 2017;**45**:255–9.

Lu MM, Wang QJ, Chang ZM *et al*. Synergistic bactericidal activity of chlorhexidineloaded, silver-decorated mesoporous silica nanoparticles. *Int J Nanomedicine* 2017;**12**:3577–89.

Macias JH, Alvarez MF, Arreguin V *et al*. Chlorhexidine avoids skin bacteria recolonization more than triclosan. *Am J Infect Control* 2016;**44**:1530–4.

Malle E, Waeg G, Schreiber R *et al*. Immunohistochemical evidence for the myeloperoxidase/H2O2/halide system in human atherosclerotic lesions. Colocalization of myeloperoxidase and hypochlorite-modified proteins. *Eur J Biochem* 2000a;**267**:4495–503.

Malle E, Waeg G, Schreiber R *et al*. Immunohistochemical evidence for the myeloperoxidase/H2O2/halide system in human atherosclerotic lesions: colocalization of myeloperoxidase and hypochlorite-modified proteins. *Eur J Biochem* 2000b;**267**:4495–503.

McNamara PJ, Levy SB. Triclosan: An instructive tale. *Antimicrob Agents Chemother* 2016;**60**:7015–6.

Miner NA, McDowell JW, Willcockson GW *et al*. Antimicrobial and other properties of a new stabilized alkaline glutaraldehyde disinfectant/sterilizer. *Am J Hosp Pharm* 1977;**34**:376–82.

Mohammed AN, Abdel Aziz SAA. Novel approach for controlling resistant Listeria monocytogenes to antimicrobials using different disinfectants types loaded on silver nanoparticles (AgNPs). *Environ Sci Pollut Res* 2019;**26**:1954–61.

Mukhomedzianova L V, Vakhrushev SG, Polevshikov AV *et al*. [Dynamics of immunological characteristics and investigation of apoptosis of palatal tonsillar lymphocytes in patients presenting with chronic tonsillitis and treated by conservative therapy]. *Vestn Otorinolaringol* 2011:13–7.

Musuuza JS, Sethi AK, Roberts TJ *et al*. Implementation of daily chlorhexidine bathing to reduce colonization by multidrug-resistant organisms in a critical care unit. *Am J Infect Control* 2017;**45**:1014–7.

Nagl M, Arnitz R, Lackner M. N-Chlorotaurine, a Promising Future Candidate for Topical Therapy of Fungal Infections. *Mycopathologia* 2018;**183**:161–70.

Nagl M, Christian M, Waldemar G *et al*. Tolerability of inhaled N-chlorotaurine versus sodium chloride in the mouse. *J Med Res Pract* 2013;**2**:2013.

Nagl M, Hengster P, Semenitz E *et al*. The postantibiotic effect of N-chlorotaurine on Staphylococcus aureus. Application in the mouse peritonitis model. *J Antimicrob Chemother* 1999;**43**:805–9.

Nagl M, Lass-Florl C, Neher A *et al*. Enhanced fungicidal activity of N-chlorotaurine in nasal secretion. *J Antimicrob Chemother* 2001;**47**:871–4.

Nagl M, Teuchner B, Pöttinger E *et al*. Tolerance of N-chlorotaurine, a new antimicrobial agent, in infectious conjunctivitis - A phase II pilot study. *Ophthalmologica* 2000;**214**:111–4.

Neher A, Nagl M, Appenroth E *et al.* Acute Otitis Externa: Efficacy and Tolerability of N-Chlorotaurine, a Novel Endogenous Antiseptic Agent. *Laryngoscope* 2004;**114**:850–4.

Normung DI fur. DIN EN 1040: Chemical Disinfectants and Antiseptics – Quantitative Suspension Test for the Evaluation of Basic Bactericidal Activity of Chemical Disinfectants and Antiseptics – Test Method and Requirements (Phase 1). *Berlin: Beuth* 2005.

O'Grady NP, Alexander M, Burns LA *et al.* Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-related Infections. *Clin Infect Dis* 2011;**52**:1087–99.

Osmanov A, Wise A, Denning DW. In vitro and in vivo efficacy of miramistin against drug-resistant fungi. *J Med Microbiol* 2019;**68**:1047–52.

Paliĭ GK, Kravets VP, Kvoal'chuk VP. [Effectiveness of sterilizing suture materials with decamethoxine]. *Klin Khir* 1991;**52**: 39–40.

Poole K. Efflux-mediated antimicrobial resistance. *J Antimicrob Chemother* 2005;**56**:20–51.

Prabhakaran S, Abu-Hasan M, Hendeles L. Benzalkonium Chloride: A Bronchoconstricting Preservative in Continuous Albuterol Nebulizer Solutions. *Pharmacotherapy* 2017;**37**: 607–10.

Pumbwe L, Skilbeck CA, Wexler HM. Induction of multiple antibiotic resistance in Bacteroides fragilis by benzene and benzene-derived active compounds of commonly used analgesics, antiseptics and cleaning agents. *J Antimicrob Chemother* 2007;**60**:1288–97.

Reyes K, Bardossy AC, Zervos M. Vancomycin-Resistant Enterococci: Epidemiology, Infection Prevention, and Control. *Infect Dis Clin North Am* 2016;**30**:953–65.

Rubbo SD, Gardner JF, Webb RL. Biocidal Activities of Glutaraldehyde and Related Compounds. *J Appl Bacteriol* 1967;**30**:78–87.

Russell AD, Path FRC. Chlorhexidine: Antibacterial action and bacterial resistance. *Infection* 1986;**14**:212–5.

Russell AD. Whither triclosan? *J Antimicrob Chemother* 2004;**53**:693–5.

Schuller-Levis GB, Park E. Taurine: new implications for an old amino acid. *FEMS Microbiol Lett* 2003;**226**:195–202.

Schwienbacher M, Treml B, Pinna A *et al.* Tolerability of inhaled N-chlorotaurine in an acute pig streptococcal lower airway inflammation model. *BMC Infect Dis* 2011;**11**:231.

Sehmi SK, Allan E, MacRobert AJ *et al.* The bactericidal activity of glutaraldehyde-impregnated polyurethane. *Microbiologyopen* 2016;**5**:891–7.

Shatrov VA, Krivoshein IS, Kovalenko V V. [The effect of miramistin on the phagocytic activity of urethral neutrophil granulocytes]. *Lab Delo* 1990:55–6.

Sheehan G, Nagl M, Kavanagh K. Exposure to N-chlorotaurine induces oxidative stress responses in Aspergillus fumigatus. *J Med Microbiol* 2019;**68**:279–88.

Sheldon AT. Antiseptic "Resistance": Real or Perceived Threat? *Clin Infect Dis* 2005;**40**:1650–6.

Silvestri DL, McEnery-Stonelake M. Chlorhexidine: uses and adverse reactions. *Dermat contact, atopic, Occup drug* 2013;**24**:112–8.

Theuretzbacher U, Van Bambeke F, Cantón R *et al.* Reviving old antibiotics. *J Antimicrob Chemother* 2015;**70**:2177–81.

Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. *Curr Opin Microbiol* 2017;**39**:106–12.

Torres-Viera C, Thauvin-Eliopoulos C, Souli M *et al.* Activities of taurolidine in vitro and in experimental enterococcal endocarditis. *Antimicrob Agents Chemother* 2000a;**44**:1720–4.

Torres-Viera C, Thauvin-Eliopoulos C, Souli M *et al.* Activities of taurolidine in vitro and in experimental enterococcal endocarditis. *Antimicrob Agents Chemother* 2000b;**44**:1720–4.

Vasil'eva T V, Raskidaĭlo AS, Arutcheva AA *et al.* [Antibacterial activity and clinical effectiveness of the new antiseptic miramistin]. *Antibiot i khimioterapiĭa = Antibiot chemoterapy [sic] / Minist meditsinskoĭ i Mikrobiol promyshlennosti SSSR* 1993;**38**:61–3.

Vieira DB, Carmona-Ribeiro AM. Cationic lipids and surfactants as antifungal agents: mode of action. *J Antimicrob Chemother* 2006;**58**:760–7.

Vozianov AF, Krivoshein IS, Pasechnikov SP *et al.* [The effect of miramistin on the phagocytic activity of the urethral neutrophilic granulocytes in patients with chronic urethroprostatitis]. *Vrach Delo* 1990:113–5.

Wand ME, Bock LJ, Bonney LC *et al.* Mechanisms of Increased Resistance to Chlorhexidine and Cross-Resistance to Colistin following Exposure of Klebsiella pneumoniae Clinical Isolates to Chlorhexidine. *Antimicrob Agents Chemother* 2017;**61**:e01162–16.

Wessels S, Ingmer H. Modes of action of three disinfectant active substances: a review. *Regul Toxicol Pharmacol* 2013;**67**:456–67.

Williamson DA, Carter GP, Howden BP. Current and Emerging Topical Antibacterials and Antiseptics: Agents, Action, and Resistance Patterns. *Clin Microbiol Rev* 2017;**30**:827–60.

Yazdankhah SP, Scheie AA, Høiby EA *et al.* Triclosan and Antimicrobial Resistance in Bacteria: An Overview. *Microb Drug Resist* 2006;**12**:83–90.

Zhou C, Wang F, Chen H *et al.* Selective Antimicrobial Activities and Action Mechanism of Micelles Self-Assembled by Cationic Oligomeric Surfactants. *ACS Appl Mater Interfaces* 2016;**8**:4242–9.

Zhukovskii VA. Problems and prospects for development and production of surgical suture materials. *Fibre Chem* 2008;**40**:208–16.

Zinchenko AA, Sergeyev VG, Yamabe K *et al.* DNA compaction by divalent cations: structural specificity revealed by the potentiality of designed quaternary diammonium salts. *ChemBioChem* 2004;**5**:360–8.

Андреева ВО, Левкович МА. Эффективность местного применения препарата мирамистин в лечении неспецифического вульвовагинита у часто болеющих девочек. *Эффективная фармакотерапия* 2016;**31**:20–6. [Andreeva VO, Levkovich MA. The effectiveness of the local drug miramistin in the treatment of non-specific vulvovaginitis in often ill girls. *Effective Pharacotheraopy*. 2016;**31**:20–6.] [Article in Russian].

Барламов ПН, Есюнина ГИ. Эффективность и безопасность применения ингаляций антисептических препаратов в комплексном лечении обострений хронических бронхитов. *Поликлиника* 2014;**5–1**:93–6. [Barlamov PN, Yesunina GI. Efficiciency and safety of the use of inhalation of antiseptic drugs in the complex treatment of exacerbations of chronic bronchintis. *Clinic*. 2014;**5-1**:96-6.] [Article in Russian].

Биткова ЕЕ, Скала Л, 3, Михайлова НА *et al.* Изучение воздействия мирамистина на кинетику роста условно-патогенных микроорганизмов в жидкой питательной среде. *Мирамистин сборник трудов под ред ЮС Кривошеина* 1995. [Bitkova EE, Skala L 3., Mikhailova NA *et al.* Study of the effects of miramistin on the kinetics of the growth of opportunistic microorganisms in a liquid nutrient medium. *Miramistin collection of workds under the editorship of US Krivoshein*. 1995.] [Article in Russian].

Блатун ЛА. Местное медикаментозное лечение ран. *Хирургия Журнал им НИ Пирогова* 2011;**4**:51–9. [Blatun LA. Local drug treatment

of wounds. *Surgery Journal named after NI Pirogov*. 2011;**4**:51-9] [Article in Russian].

Бойко НВ, Калинкина МИ, Горшкова ГИ. Консервативное лечение хронического тонзиллита. *Детская оториноларингология* 2012;**3**:22–4. [Boyko NV, Kalinkina MI, Gorshkova GI. Conservative treatment of chronic tonsilitis. *Children's otorhinolaryngology*. 2012;**3**:22–4.] [Article in Russian].

Будзинский НЭ, Сирак СВ. Особенности лечения хронического верхушечного периодонтита с использованием мирамистина, иммобилизованного на композиционном полисорбе. *Современные проблемы науки и образования* 2013;**3**:133. [Budzinskii NE, Syrac NE. Features of the treatment of chronic apical periodontitis using miramistin immoblised on composite polysorb. *Modern problems of science and education*. 2013;**3**:133.] [Article in Russian].

Габидулина ТВ, Тимошина ЕЛ, Юрьев СЮ *et al*. Влияние урогенитальных инфекций на течение беременности и состояние плода и новорожденного. *Бюллетень сибирской медицины* 2002;**1**:84–8. [Gabidulina TV, Timoshine EL, Yuryev SJ *et al*.. The effect of urogenital infections on pregnancy and the condition of the fetus and newbron. *Siberain Medicine Bulletin*. 2002;**1**:84–8.] [Article in Russian].

Гордиенко АИ, Филатов АС. Электрофорез с мирамистином в профилактике гнойных раневых осложнений после аппендэктомии. *Вестник физиотерапии и курортологии* 1997;**4**:47–9. [Gordienko AI, Filatov AS. Electrophoresis with miramistin in the prevention of purulent wound complications after appendectomy. *Bulletin of physiotherapy and balneology*. 1997;**4**:47–9.] [Article in Russian].

Григорьян АЮ, Кобзарева ЕВ, Горохова АС *et al*. Антисептик мирамистин в лечении гнойных ран. *Сборник научных трудов Sworld* 2014;**33**:49–53. [Grigoryan AJ, Kobzareva EB, Gorokhova AS *et al*.. Miramistin antiseptic in the treatment of purulent wounds. *Collection of scientific works of Sworld*. 2014;**33**:49–53.] [Article in Russian].

Данилова ТА, Данилина ГА, Аджиева АА *et al*. Влияние мирамистина и фосфренила на микробные биопленки. *Бюллетень экспериментальной биологии и медицины* 2017;**4**:435–9. [Danilova TA, Danilina GA, Adzhieva AA *et al*.. The effect of miramistin and fosprenil on microbial biofilms. *Bulletin of Experimental Biology and Medicine* 2017;**4**:435–9.] [Article in Russian].

Девдера ОІ, Нідзельський МЯ, Цебржинський ОІ. Ефективність очищення і дезинфекція зубних протезів в клінічних умовах. *Проблемы экологии и медицины* 2008;**12**:37–9. [Devdera OI, Niedzelskiy ME, Tsebrzynsky OI. Efficiency of cleaning and disinfection of dentures in clinical settings. *Problems of Ecology and Medicine*. 2008;**12**:37–9.] [Article in Russian]

Дунаевский АМ, Кириченко ИМ. Клиническое обоснование использования препарата МИРАМИСТИН в терапии инфекционно-воспалительных заболеваний респираторной системы. *Поликлиника* 2013;**5**:1–11. [Dunaevsky AM, Kirichenko IM. Clinical rationale for the use of the drug MIRAMISTIN in the treatment of infectious and inflammatory diseases of the respiratory system. *Clinic*. 2013;**5**:1–11.] [Article in Russian]

Завалий МА. Применение мирамистина в комплексном лечении больных с различными формами синусита. *Журнал вушних носових і горлових хвороб* 1997;**6**:38–42. [Zavaliy MA. The use of miramistin in the complex treatment of patients with various forms of sinusitis. *Magazine of the Nose and Throat Twigs*. 1997;**6**:38–42.] [Article in Russian]

Иванова НВ, Боброва НФ, Кривошеин ЮС. Клиническая эффективность применения мирамистина в комплексном лечении больных хроническими конъюнктивитами. *Офтальмологический журнал* 1999;**3**:163–70. [Ivanova NV, Bobrova NF, Krivoshein U.S. Clinical efficacy of miramistin in the complex treatment of patients with chronic conjunctivitis. *Ophthalmological Journal*. 1999;**3**:163–70.] [Article in Russian]

Кайгородцев ВВ, Коркмазов МЮ. Об эффективности и целесообразности медикаментозных препаратов в терапии инфекционных наружных отитов. *Вестник челябинской областной клинической больницы* 2012;**4**:31–4. [Kaygorodtsev VV, Korkmazov MJ. On the effectiveness and feasibility of drugs in the treatment of infectious otitis externa. *Bulletin of the Chelyabinsk Regional Clinical Hospital*. 2012;**4**:31–4.] [Article in Russian]

Калантаров ГК. Особенности течения катарального гингивита на фоне лечения мирамистином. *Журнал научных статей здоровье и образование в XXI веке* 2012;**14**:118–20. [Kalantarov GK. Features of the course of catarrhal gingivitis during treatment with miramistin. *Journal of Scientific Articles Health and Education in the 21st Century*. 2012;**14**:118–20.] [Article in Russian]

Кириченко ИМ. Использование препарата Мирамистин при инфекционной патологии в гинекологии. *Поликлиника* 2013;**6**:100–2. [Kirichenko I.M. The use of the drug Miramistin for infectious diseases in gynecology. *Clinic*. 2013;**6**:100–2.] [Article in Russian]

Криворутченко ЮЛ, Кривошеин ЮС, Маренникова СС *et al*. Изучение анти-ВИЧ-активности мирамистина. *Вопросы вирусологии* 1994;**6**:297–69. [Krivorutchenko Yu.L., Krivoshein Yu.S., Marennikova SS *et al*.. The study of anti-HIV activity of miramistin. *Virology Issues*. 1994;**6**:297–269.] [Article in Russian]

Криворутченко ЮЛ. Инактивация мирамистином вируса иммунодефицита человека. *Журн дерматол и венерол* 1990;**1**:22–4. [Krivorutchenko Yu.L. Miramistin inactivation of human immunodeficiency virus. *Jurn Dermatol and Venerol*. 1990;**1**:22–4.] [Article in Russian]

Криворутченко ЮЛ. Чувствительность к мирамистину, амфотерицину в и таурозиду Sx1 грибов, выделенных от больных в Крыму. *Biomed Biosoc Anthropol* 2010:144–9. [Krivorutchenko Yu.L. Sensitivity to miramistin, amphotericin B and tauroside Sx1 fungi isolated from patients in the Crimea. *Biomed Biosoc Anthropol*. 2010:144–9.] [Article in Russian]

Кривошеин ЮС, Рудько АП. Мирамистин и инфекции передаваемые половым путем. *Использование Препарата Мирамистин в Лечебно-Профилактических Учреждениях г. Москвы*; Москва, 2003. [Krivoshein U.S., Rudko AP. Miramistin and sexually transmitted infections. *Use of the Miramistin Preparation in Medical and Prevention Institutions of Moscow*. Moscow, 2003.] [Article in Russian]

Кривошеин ЮС ed. *Мирамистин. Сборник Трудов*. Москва: Медицинское информационное агентство; 2004. [Krivoshein US ed. Miramistin. Proceedings. Moscow: Medical News Agency, 2004.] [Article in Russian]

Крутиков СН, Криворутченко ЮЛ, Кривошеин ЮС *et al*. Применение мирамистина в лечении грибково-бактериального перитонита у больной, находящейся на перитонеальном диализе. *Успехи медицинской микологии* 2004:226–7. [Krutikov SN, Krivorutchenko Yu.L., Krivoshein Yu.S. *et al*.. The use of miramistin in the treatment of fungal-bacterial peritonitis in a patient undergoing peritoneal dialysis. *Advances in Medical Mycology*. 2004:226–7.] [Article in Russian]

Крюков АИ, Кунельская ВЯ, Ивойлов АЮ *et al*. Клиническая эффективность применения препарата Мирамистин у детей с обострением хронического грибкового аденоидита. *Лечебное дело* 2016;**4**:45–50. [Kryukov AI, Kunelskaya VY, Ivoylov AY *et*

al.. Clinical efficacy of the use of Miramistin in children with exacerbation of chronic fungal adenoiditis. *General Medicine*. 2016;**4**:45–50.] [Article in Russian]

Кунельская ВЯ, Мачулин АИ Особенности патогенеза и терапии грибковых аденоидитов в детском возрасте. *Успехи медицинской микологии* 2013;**11**:236–8. [Kunelskaya VY, Machulin AI. Features of the pathogenesis and therapy of fungal adenoiditis in childhood. *Advances in Medical Mycology*. 2013; **11**:236–8.] [Article in Russian]

Курдекбаев КК. Антибактериальная терапия у больных с синдромом диабетической стопы. *Вестник Казахского Национального медицинского университета* 2013;**1**:226–7. [Kurdekbaev KK. Antibacterial therapy in patients with diabetic foot syndrome. *Bulletin of the Kazakh National Medical University*. 2013;**1**:226–7.] [Article in Russian]

Кустов ОИ. Опыт использования препарата мирамистин в комплексной терапии пациентов с острыми обострением хронического ларингита в условиях амбулаторно-поликлинического приёма. *Поликлиника* 2015;**3**:124–5. [Kustov OI. The experience of using the drug miramistin in the treatment of patients with acute exacerbation of chronic laryngitis in an outpatient setting. *Polyclinic*. 2015;**3**:124–5.] [Article in Russian]

Логинов ЛП, Кривошеин ЮС, Шахламов МВ. Местное лечение обожженных отечественным антисептиком мирамистином. *Тез. Докл. Межд. Конференции ≪Актуальные Проблемы Термической Травмы≫*. С.Петербург, 2002. [Loginov LP, Krivoshein U.S., Shakhlamov MV. Local treatment burnt with domestic antiseptic miramistin. *Thes. Doc. Int. Conferences "Actual Problems of Thermal Trauma"*. S. Petersburg, 2002.] [Article in Russian]

Ляпунов НА, Пуртов АВ, Дунай ЕВ. Поверхностно-активные, коллоидно-мицеллярные и антибактериальные свойства некоторых катионных антисептиков. *Фармация* 2013:44–7. [Lyapunov NA, Purtov AB, Danube EB. Surface-active, colloidal micellar and antibacterial properties of some cationic antiseptics. *Pharmacy*. 2013:44–7.] [Article in Russian]

Майчук ЮФ, Селивёрстова КЕ, Якушина ЛН. Антисептик окомистин в лечении бактериальных заболеваний глаз. *Катарактальная и рефракционная хирургия* 2011;**11**:59–64. [Maychuk Law Firm, Seliverstova KE, Yakushina LN. Antiseptic ocomistin in the treatment of bacterial eye diseases. *Cataract and refractive surgery*. 2011;**11**:59–64.] [Article in Russian]

Милявский АИ, Кривошеин ЮС, Лагодырь ТА *et al*. Эффективность применения отечественного антисептика мирамистина в дерматовенерологии. *Вестник дерматологии и венерологии и венерологии* 1996;**2**:67–9. [Milyavsky AI, Krivoshein Yu.S., Lagodyr TA *et al*.. The effectiveness of the use of domestic antiseptic miramistin in dermatovenereology. *Bulletin of Dermatology and Venereology and Venereology*. 1996;**2**:67–9.] [Article in Russian]

Молочное ЕВ, Арзуманян ВА, Кириченко ИМ *et al*. Изучение противогрибкового действия препаратов Мирамистина in vitro и эффективность их применения в дерматологии. *ММА им И М Сеченова, НИИ вакцин и сывороток им, И И Мечникова РАМН* 2003. [Molochnoye EB, Arzumanyan VA, Kirichenko IM *et al*.. Studying the antifungal effect of Miramistin preparations in vitro and the effectiveness of their use in dermatology. *MMA named after IM Sechenov, Research Institute of Vaccines and Serums named after IM, Mechnikov RAMS*. 2003.] [Article in Russian]

Нехороших ЗН, Маликова МВ, Кривошеин ЮС *et al*. Применение мирамистина в комплексном этиопатогенетическом лечении урогенитального хламидиоза. *Тез Докл VII Рос Нац Конгресса "Человек и Лекарство" Москва* 2000:303. [Nechoroshikh ZN, Malikova MV, Krivoshein U.S. *et al*.. The use of miramistin in the complex etiopathogenetic treatment of urogenital chlamydia. *Thes. Doc. VII Ros. Nat Congress "Man and Medicine."* Moscow, 2000:303.] [Article in Russian]

Попов ДА, Анучина НМ, Терентьев АА *et al*. Диоксидин: антимикробная активность и перспективы клинического применения на современном этапе. *Антибиотики и химиотерапия* 2013;**58**:37–42. [Popov DA, Anuchina NM, Terentyev AA *et al*.. Dioxidin: antimicrobial activity and prospects for clinical use at the present stage. *Antibiotics and chemotherapy*. 2013;**58**:37–42.] [Article in Russian]

Рищук СВ, Гусев СН, Душенкова ТА. Использование препарата "мирамистин" при репродуктивно значимой инфекционной патологии. *Terra Medica* 2012;**1**:18–24. [Rischuk SV, Gusev SN, Dushenkova TA. The use of the drug "miramistin" with reproductive significant infectious pathology. *Terra Medica*. 2012; **1 (67)**:18–24.] [Article in Russian]

Самохина ВИ, Чеснокова МГ, Ландинова ВД *et al*. Возможности эффективной эрадикации микроорганизмов корневого канала посредством медикаментозной эндодонтической обработки. *Эндодонтия Today* 2013;**3**:22–8. [Samokhina VI, Chesnokova MG, Landinova VD *et al*.. Possibilities of effective eradication of root canal microorganisms through drug endodontic treatment. *Endodontics Today*. 2013;**3**:22–8.] [Article in Russian]

Свистов ЕВ. *Отчет о Доклинических и Клинических Исследованиях Препарата Мирамистин Раствор Для Местного Применения 0,01%*. Москва, 2003. [Svistov EV. *Report on preclinical and clinical studies of the drug Miramistin Topical Solution 0.01%*. Moscow, 2003.] [Article in Russian]

Смирнов СВ, Логинов ЛП, Шахламов МВ. Опыт использования отечественного антисептика мирамистина в лечении ожоговых больных. *Тез. Докл. I-Ой Междунар. Конф. ≪Клинические Исследования Лекарственных Средств≫*. Москва, 2002. [Smirnov SV, Loginov LP, Shakhlamov MV. The experience of using domestic antiseptic miramistin in the treatment of burn patients. *Thes. Doc. I-International Conf. "Clinical Drug Research."* Moscow, 2002.] [Article in Russian]

Сытник АН, Шидловский ВА. Профилактика гнойных заболеваний кисти и пальцев мирамистином после микротравм на производстве. *Актуальные Вопросы Микробиологии, Эпидемиологии и Иммунологии Инфекционных Болезней;*. Харьков, 1993:333. [Sytnik AN, Shidlovsky VA. Prevention of purulent diseases of the hand and fingers with miramistin after microtraumas at work. *Actual Issues of Microbiology, Epidemiology and Immunology of Infectious Diseases*. Kharkov, 1993:333.] [Article in Russian]

Фахер С. *Применение антисептика мирамистина для индивидуальной профилактики и лечения некоторых венерических болезней*. 1991. [Facher S. Application of the Miramistin antiseptic for individual prophylaxis and treatment of certain sexually transmitted diseases. 1991.]

Флейшер ГМ. Оценка эффективности комплексного лечения кандидоза слизистой оболочки полости рта с применением мирамистина. *Стоматолог-практик* 2015;**4**:27–31. [Fleisher GM. Evaluation of the effectiveness of complex treatment of candidiasis of the oral mucosa using miramistin. *Practicing Dentist*. 2015;4 (254):27–31.] [Article in Russian]

Фролова АВ, Косинец АН. Сравнительная оценка антимикробной активности традиционных антисептиков и растительного средства ≪фитомп≫ в отношении возбудителей хирургической инфекции. *УО "Витебский государственный медицинский*

университет" 2008. [Frolova AV, Kosinets AN. Comparative evaluation of the antimicrobial activity of traditional antiseptics and the herbal remedy "phytomp" against pathogens of surgical infection. *EE "Vitebsk State Medical University"*. 2008.] [Article in Russian]

Хан МА, Лян НА, Вахова ЕЛ *et al*. Ингаляции мирамистина при острых респираторных заболеваниях у детей. *Вопросы курортологии, физиотерапии и лечебной физической культуры* 2015;**92**:35–9. [Khan MA, Liang NA, Wahova EL *et al*.. Miramistin inhalation in acute respiratory infections in children. *Issues of balneology, physiotherapy and physiotherapy*. 2015;**92**:35–9.] [Article in Russian]

Шабалдина ЕВ, Рязанцев СВ, Шабалдин АВ. Эффективность применения мирамистина у детей раннего и дошкольного возраста с гипертрофией миндалин лимфоидного глоточного кольца, с рецидивирующими острыми респираторными инфекциями и сенсибилизацией к streptococcus pyogenes. *Педиатрия журнал им ГН Сперанского* 2015;**94**:96–104. [Shabaldina EV, Ryazantsev SV, Shabaldin AB. The effectiveness of miramistin in children of early and preschool age with hypertrophy of the tonsils of the lymphoid pharyngeal ring, with recurrent acute respiratory infections and sensitization to streptococcus pyogenes. *Pediatrics Journal named after GN Speransky*. 2015;**94**:96–104.] [Article in Russian]

Шпилевой АИ, Сегалов ВМ, Филатов АС. Применение мирамистина в комплексном лечении больных разлитым перитонитом. *Актуальные Вопросы Микробиологии, Эпидемиологии и Иммунологии Инфекционных Болезней: Тезисы Докладов Украинской Республиканской Конференции*; Харьков, 1993:388. [Shpileva AI, Segalov VM, Filatov AS. The use of miramistin in the complex treatment of patients with diffuse peritonitis. Actual Issues of Microbiology, *Epidemiology and Immunology of Infectious Diseases: Abstracts of the Reports of the Ukrainian Republican Conference*. Kharkov, 1993:388.] [Article in Russian]