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 LD50 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
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 1980s 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; Musuza 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 (Daniilova 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 (Joannou, 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; Joannou, 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 (Zinchenco 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 Molochnye 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.
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. apiospernum, 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 и соавтор] 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, furacin, 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 и 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 Молочноyе et al. (2003).

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC range (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida spp.</td>
<td>15 -100</td>
</tr>
<tr>
<td>Trichophyton spp.</td>
<td>100–500</td>
</tr>
<tr>
<td>T. mentagrophytes</td>
<td>30</td>
</tr>
<tr>
<td>Malassezia spp.</td>
<td>1000–5000</td>
</tr>
<tr>
<td>M. sympodialis</td>
<td>100–500</td>
</tr>
<tr>
<td>Rhodotorula spp.</td>
<td>1–60</td>
</tr>
<tr>
<td>Cryptococcus spp.</td>
<td>1–60</td>
</tr>
<tr>
<td>Trichosporon spp.</td>
<td>1–60</td>
</tr>
</tbody>
</table>

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 Kryuchenko 2013) [Криворутченко 1990; Криворутченко et al. 1994; Дунаевский и Кириченко 2013]. There are some old data on miramistin activity for coronaviruses (Криворутченко 1990; Криворутченко et al. 1994; Дунаевский и 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®) (Крutyakov et al. 2016). Promising clinical results in dogs suggest possible use of Argumistin® in humans but more research is required (Крutyakov 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. typhimurium from B. Ames collection. Results have shown that miramistin does not exhibits direct mutagenic properties (1993). Fromm-Dornien et al. (2015) have...
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 cetypyridinium 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\textsubscript{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\textsubscript{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\textsubscript{50} 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 Genni 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 Genni 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) 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 (Grabinska-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 (Молочко et al. 2003) and wound infection management (Sytinik and Shidlovskyi 1993; Grigor’yan et al. 2014) [Сытин и Шидловский 1993; Григорьян et al. 2014]. Miramistin was also used in the management of burns (Loginov, Krivoshein and Shakhalamov 2002; Smirnov, Loginov and Shakhalamov 2002) [Логинов, Кривошеин и Шахламов 2002; Смирнов, Логинов и 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; Mayuchuk, Selivorostova and Yakushina 2011) [Иванова, Боброва и Кривошеин 1999; Майчук, Селиверстова и 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 и Левкович 2016]. There is also experience of postcoital prophylaxis of STDs in men and women (Milyavskiy et al. 1996; Rischchuk, Gusev and Dushenkova 2012) [Мильяский et al. 1996; Ришчук, Гусев и 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) [Некороших et al. 2000; Габидуллина et al. 2002].

In dentistry, clinical experience includes treatment of gingivitis (Kalantarov 2012) [Каланторов 2012] and use as a component of root canal fillings (Budzinskiy and Syrca 2013; Samokhina et al. 2013) [Будзинский и Сырся 2013; Самохина et al. 2013]. There is clinical experience of irrigation with miramistin solution for treatment of nasopharyngitis and tonsillitis (Zavaly 1997; Kustov 2015) [Завалий 1997; Кустов 2015]. In children, miramistin was used for irrigation of mucus during rhinitis and tonsillitis (Kunel’skaya and Machulin 2013; Shirabaldina, Ryazantsev and Shabaldin 2015; Kryukov 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, Kalinkinka and Gorshikova 2012; Barlamov and Yesyunina 2014; Shirabaldina, Ryazantsev and Shabaldin 2015) [Бойко, Калининка и Горшкова 2012; Барлаамов и Есюнина 2014; Шира́бальдина, Рязанцев и Шабалин 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 microbota, plants and fish, and emerging cross-resistance with antibiotics (Barra Caracciolo, Topp and Genni 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, as nose decongestant lotions, facial cleansers, acne treatment, ammonium compounds and has broad antimicrobial activity. Benzalkonium chloride belongs to the group of quaternary ammonium compounds. Benzalkonium chloride is mainly used as a cytotoxicant in anaerobic environments due to the 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; Popov et al. 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; Popov 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 methyl 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 Nagli 2010). NCT has shown efficacy in chronic leg ulcers with purulent coating external otitis and bacterial and viral conjunctivitis (Nagli et al.
Glutaraldehyde

Glutaraldehyde is a saturated dialdehyde that has gained wide acceptance as a disinfectant and chemical sterilant. Since its introduction in the early 1960s, 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 sulphhydril, 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 colleagues 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 dermatothyes and Candida spp. In early studies, Aspergillus niger was more resistant than other fungi to glutaraldehyde (Rubbo, Gardner and Webb 1967; Gorman, Scott and Russell 1980). More recent work has shown that glutaraldehyde in solution, caused a 105 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 Russell 1980)). One important proviso is that papovaviruses and parvoviruses might be somewhat resistant to chemical inactivation.
<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>Class</th>
<th>Mode of Action</th>
<th>Antimicrobial spectrum</th>
<th>Clinical use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miramistin</td>
<td>Quaternary ammonium compound</td>
<td>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.</td>
<td>Broad activity against bacteria, viruses, and fungi.</td>
<td>Wound and burn management, Rhinitis, sinusitis and tonsillitis, Otitis externa, Conjunctivitis, Vaginitis, Postcoital prevention of STDs</td>
<td>Resistance is uncommon. Activity against resistant fungal strains</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Divalent cationic biguanide</td>
<td>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</td>
<td>Most active against Gram-positive, also against Gram-negative, fungi, and some enveloped viruses</td>
<td>Skin and mucosa decontamination and disinfection, Wound management, Component of mouthwashes</td>
<td>Widely used to prevent healthcare-associated infections, Mixed evidence on resistance</td>
</tr>
<tr>
<td>Triclosan</td>
<td>Bisphenol</td>
<td>Binds to the protein complex Fabl or InhA resulting in the inhibition of fatty acid synthesis</td>
<td>Broad activity against bacteria, also possesses some activity against viruses and fungi</td>
<td>Disinfectant or preservative in consumer products, Impregnation of medical devices</td>
<td>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.</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>Quaternary ammonium compound</td>
<td>Alteration of the membrane and changes in charge distribution which leads to denaturation of membrane proteins leading to cytoplasmic leakage</td>
<td>Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, and a sporicidal activity</td>
<td>Skin disinfection, Wound management, Preservative in pharmaceutical products including such as eye, ear and nasal drops</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Continued

<table>
<thead>
<tr>
<th>Antiseptic</th>
<th>Class</th>
<th>Mode of Action</th>
<th>Antimicrobial spectrum</th>
<th>Clinical use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decamethoxin</td>
<td>Bis-quaternary ammonium compound</td>
<td>Accumulates in microbial cytoplasmatic membranes and binds to the phosphate groups of membrane lipids leading to a decrease in permeability of the cytoplasmic membrane</td>
<td>Broad-spectrum microbicidal activity against bacteria, fungi, and viruses</td>
<td>Skin decontamination and disinfection</td>
<td>Irrigation of peritoneal cavity during surgery Disinfection of medical devices</td>
</tr>
<tr>
<td>Dioxidine Quinoxaline derivatives</td>
<td>Inhibition of DNA synthesis and alteration of DNA integrity</td>
<td>Broad antibacterial activity including anaerobes</td>
<td>Wound management</td>
<td>Concerns over dioxidine inducing cross-resistance with antibiotics</td>
<td></td>
</tr>
<tr>
<td>Taurolidine</td>
<td>Aminosulfonic acid taurine derivative</td>
<td>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</td>
<td>Gram-positive bacteria, Gram-negative bacteria, anaerobes and fungi</td>
<td>Pleural and peritoneal decontamination during surgery Impregnation of catheters</td>
<td></td>
</tr>
<tr>
<td>N-chlorotaurine</td>
<td>Taurine derivative</td>
<td>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</td>
<td>Broad activity against bacteria, viruses, parasites, and fungi</td>
<td>Wound management</td>
<td>Has anti-inflammatory properties</td>
</tr>
<tr>
<td>Glutaraldehyde</td>
<td>Saturated dialdehyde</td>
<td>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</td>
<td>Gram-positive and Gram-negative bacteria, fungi, enveloped viruses, and sporicidal activity</td>
<td>Has anti-inflammatory properties</td>
<td>Resistance is uncommon Activity against resistant fungal strains</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Possible indication</th>
<th>Current practice(s)</th>
<th>Clinical experience of using miramistin for this purpose (references)</th>
<th>Comments on using miramistin for this purpose</th>
</tr>
</thead>
</table>
| 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 и 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                                | Yes (Loginov, Krivoshein and Shakhlamov 2002; Smirnov, Loginov and Shakhlamov 2002) [Логинов, Кривошеин и Шахламов 2002; Смирнов, Логинов и Шахламов 2002] |                                                                                                                                   |                                                                                                                                   |
| Prevention of upper respiratory tract infections | Cetylpypyridinium chloride                                                          | No                                                                                                                                |                                                                                                                                   |
| Oral mucosal infections, notably candidiasis    | Chlorhexidine                                                                       | Yes (Kalantarov 2012; Kuneľ'skaya and Machulin 2013; Fleischer 2015; Shabaldina, Ryazantsev and Shabaldin 2015; Kryukov et al. 2016) [Калантаров 2012; Кунельская и Мачулин 2013; Флейшер 2015; Шабалдина, Рязанцев и 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 и Кормазов 2012]                                                            |                                                                                                                                   |
| Fungal keratitis                                | Systemic antifungals  
Topical antifungals                                                                 |                                                                                                                                   |                                                                                                                                   |
| Conjunctivitis (empiric treatment), antimicrobial prophylactics in eye injuries | Systemic antimicrobials  
Topical antimicrobials and antiseptics                                                                 | Yes (Ivanova, Bobrova and Krivoshein 1999; Maychuk, Selivostova and Yakushina 2011) [Иванова, Боброва и Кривошен 1999; Майчук, Селивёрстова и 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; Andrejeva and Levkovich 2016) [Кириченко 2013; Андреева и Левкович 2016] |                                                                                                                                   |
| Intra-abdominal surgical wash                   | Various antiseptics  
Antibiotic instillation and systemic antibiotics or antifungals                                                                 | Yes (Shipilev, Segalov and Filatov 1993; Gordiyenko and Filatov 1997) [Шпилевой, Сегалов и Филатов 1993; Гордиенко и Филатов 1997] |                                                                                                                                   |
| Chronic ambulatory peritoneal dialysis-related peritonitis | Antibiotic instillation and systemic antibiotics or antifungals  
Hand/skin decontamination | Yes, in one patient (Krutikov et al. 2004) [Крутиков et al. 2004]                                                               |                                                                                                                                   |
| Nasal decontamination for prevention of surgical site infection | Various antiseptics, mainly chlorhexidine  
Chlorhexidine                                                                 | No                                                                                                                                |                                                                                                                                   |
### Table 5. Continued

<table>
<thead>
<tr>
<th>Possible indication</th>
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<th>Clinical experience of using miramistin for this purpose (references)</th>
<th>Comments on using miramistin for this purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal and human bites</td>
<td>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</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Postcoital prophylaxis of STDs</td>
<td>Empiric antimicrobial prophylaxis for chlamydia, gonorrhoea, and trichomonas Individualized HIV PEP HPV vaccination Postexposure HBV vaccination Rabies and tetanus vaccination may be necessary</td>
<td>Yes (Milyavskiy et al. 1996; Rishchuk, Gusev and Dushenkova 2012) [Милявский et al. 1996; Рищук, Гусев and Душенкова 2012]</td>
<td></td>
</tr>
<tr>
<td>Superficial infections with non-dermatophyte moulds</td>
<td>Topical antifungals, although resistance to terbinafine is emerging</td>
<td>No</td>
<td>Active against non-dermatophyte moulds</td>
</tr>
<tr>
<td>Nebulized solution for fungal asthma (ABPA and SAFS) and Aspergillus trachobronchitis or antifungal prophylaxis Inclusion into root canal filings/irrigation</td>
<td>Antifungals, especially amphotericin B</td>
<td>Not for this purpose, but it was used as a nebulized solution (Xin et al. 2015)</td>
<td>May potentially lead to bronchospasm in some patients</td>
</tr>
<tr>
<td>Impregnation onto catheters/medical devices</td>
<td>Calcium hydrochloride/chlorhexidine as component of filling Natrium hyochlorite, alcohol, or chlorhexidine for irrigation</td>
<td>Yes (Samokhina et al. 2013; Budzinskii and Syrac 2013) [Самохина et al. 2013; Будзинский and Сирак 2013]</td>
<td>High concentration may be used for this purpose</td>
</tr>
<tr>
<td>Impregnation onto surgical sutures</td>
<td>Impregnation with antiseptics, particularly chlorhexidine</td>
<td>Yes (Budzinskii and Syrac 2013) [Будзинский and Сирак 2013]</td>
<td></td>
</tr>
<tr>
<td>Impregnation onto silver nanoparticles</td>
<td>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, chlorhexidine, hydrogen peroxide and sodium hypochlorite) (Lu et al. 2017, Mohammed and Abdel Aziz 2019)</td>
<td>Yes (Krutyakov et al. 2016)</td>
<td>Pre-cinical experience (Krutyakov et al. 2016)</td>
</tr>
<tr>
<td>Incorporation into anti-microbial fabrics</td>
<td>Silver nanoparticles without antiseptics; Silver nanoparticles impregnated with antiseptics, mainly QACs</td>
<td>Yes (Devdera, Nidzel’s’kyy and Tserbrzhyns’kyy 2008) [Девдера, Нідзельський and Цєбржинський 2008]</td>
<td></td>
</tr>
<tr>
<td>Medical device decontamination</td>
<td>Various antiseptics, mainly chlorhexidine Hydrogen peroxide</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Surface decontamination</td>
<td>Various compounds including Virosolve, Vircon, quaternary ammonium compounds, and benzalkonium chloride</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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 sulfamethoxazol, ampicillin, and cefotaxime is one example (Kampf 2018). Another example is chlorhexidine cross-resistance with sulfamethoxazol, cefazidime, tetracycline, cefotaxime, and imipenem (Braoudaki and Hilton 2004; Pumbwe, Skilbeck and Wexler 2007; Knapp et al. 2013; Wand et al. 2017). Cross-resistance to sulfamethoxazol, cefotaxime, ceftazidime, and chloramphenicol sulfamethoxazol, cefotaxime, ceftazidime, and chloramphenicol was also found with octenidine, didecylmethylammonium chloride, sodium hypochlorite, and triclosan (Kampf 2018). The second trend is emerging resistance to antiseptics among MRSA (Hughes and Ferguson 2017; Williamson, Carter and Howden 2017) and decreased susceptibility of C. auris biofilms (Kean et al. 2018).

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

Possible uses of miramistin

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

Further clinical studies

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

CONCLUSION

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

SUPPLEMENTARY DATA

Supplementary data are available at FEMSRE online.

ETHICAL APPROVAL

Ethical approval is not required.

ACKNOWLEDGMENTS

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