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Word count for the Abstract: 123

Word count for the body of the text: 1264

Number of references: 10

Number of Table: 1

AUTHOR CONTRIBUTION

AC was involved in the writing of the text; EB was involved in the concept of the study and in the reviewing of the text; GD was involved in the concept of the study, in the research of sponsors, and in the reviewing of the text.

DISCLOSURE OF CONFLICT OF INTEREST

Mylan pharmaceutical laboratory partially funded this study and provided free-of-charge the antiseptic vials.

ABSTRACT

Candida auris is an emerging yeast pathogen with worldwide distribution and a great propensity for nosocomial spread. Recent reports have warned of the significant emergence of *C. auris* in several healthcare facilities. In order to stop its nosocomial transmission, use of antiseptics constitutes the first-line lever of action in the fighting against *C. auris* skin colonization. However, little is known about the efficacy of these products, and moreover no antiseptics are currently registered for use against *C. auris*. This study investigated the *in vitro* yeasticidal activity of povidone-iodine against *C. auris*, and compared the findings to *C. albicans* and *C. glabrata*, according to the EN standard 1275:2005. Results support the use of such commercial antiseptics in the context of colonization with this yeast.

Key words: *Candida auris*, povidone-iodine, EN 1275

Dear Editor,

First isolated from the external ear canal of a Japanese patient in 2009[1], *Candida auris* is an emerging yeast pathogen that has been put in the spotlight over the last decade as a global health threat; this species has been associated with multiple nosocomial outbreaks in several healthcare facilities worldwide, both in colonization and invasive infection cases[2], and is sometimes challenging for its identification[3] and for choosing the adequate antifungal therapy because of elevated minimal inhibition concentrations (MICs)[4]. However, accurate data are still lacking about *C. auris*, especially about its sensitivity to antiseptics that are usually supposed to play a critical role in the fight against nosocomial transmission.

Chlorine-based surface disinfectants and improved hydrogen peroxide disinfectants were already demonstrated to be highly active against *Candida* species, including *C. auris*[6,7] (at the opposite of quaternary ammonium disinfectants[6]), according to the European and International Standards EN 13624:2013 and ASTM E2197-11. Nevertheless, no commercial disinfectant product has been officially registered so far by the health authorities for specific use against *C. auris*. Data appear even more limited about the yeasticidal activity of antiseptics: only a chlorhexidine-based product [chlorhexidine 2% (w/v) chlorhexidine gluconate in 70% (v/v)] and an iodine-based antiseptic [10% (v/v) povidone-iodine] were shown effective so far, against *C. auris*, according to the European Standard EN 13624:2013[7]. Thus, the aim of this study was to assess the *in vitro* yeasticidal activity of three different iodine-based antiseptic products against *C. auris.*

The isolate of *C. auris*, number 171 10744, was obtained from a 58 year-old-Lebanese man who had been hospitalized for liver transplantation[3] (clinical collection of the Parasitology-Mycology laboratory of Tours University Hospital, France). Species identification was confirmed by MALDI-TOF mass spectrometry and DNA sequencing[3]. *C. auris* suspensions were obtained on malt extract media (PO 5055 A, OXOID, Hampshire, UK) [8], and prepared to yield a final organism density comprised between 1.5×10^7 and 5.0×10^7 colony-forming units *per* milliliter (CFU/mL). The products to be tested included three commercial 'ready-to-use' povidone-iodine-based antiseptics: one foaming solution for cutaneous application [4% (w/v) povidone-iodine; MEDA PHARMA, Paris - France] named Betadine Scrub 4%® for preoperative hand washing or antiseptic washing, and two solutions for cutaneous application [10% (w/v) povidone-iodine; MEDA PHARMA, Paris - France] referred to as Betadine dermique 10%® used for the antisepsis of healthy or damaged skin and mucous membranes, and [5% (w/v) povidone-iodine, in 70% (v/v) ethanol 96%; MEDA PHARMA, Paris - France] so called Betadine alcoolique 5%® used for surgical or skin antisepsis before minor surgery. All the aforementioned products were diluted with water for injection for the testing procedure: at 80% for all three, then at 0.25% for Betadine Scrub 4%®, at 0.10% for Betadine dermique 10%®, and at 2% for Betadine alcoolique 5%®. The method for evaluating the yeasticidal efficacy was based on a quantitative dilution-neutralization testing according to the EN 1275:2005 standard[8].

All the iodine-based antiseptics, at a concentration of 80% (as recommended by EN 1275:2005 standard[8]), decreased *C. auris* viability to below the limit of efficiency defined for antiseptics[8], achieving >4 Log_{10} reduction (Table 1). Yeasticidal concentrations were even largely lower for Betadine scrub® and alcoholic Betadine alcoolique®, at 0.25% and 2% respectively. Same kind of tests were carried out on the *Candida albicans* ATCC 10231 reference strain and exhibited similar efficiency of the iodine-based antiseptics (Table 1). As for *C. auris*, Betadine dermique® showed lower yeasticidal concentrations for *C. albicans* at 0.1%. In addition, *C. glabrata* (*i.e.* a yeast species of clinical interest and which has proved problematic in surgical intensive care departments) was also tested and actually found less susceptible to povidone-iodine antiseptics than *C. auris*: for instance following 15 min contact with Betadine Scrub® diluted at 0.25%, the yeast survival rate was only 0.07% for *C. auris vs.* 1.5% for *C. glabrata* ATCC MYA2950 reference strain, and 0.25% for the clinical strains; for Betadine alcoolique®, only 0.02% for *C. auris vs.* 1.8% for *C. glabrata* reference strain and 0.36% for the clinical strains; and eventually for Betadine dermique®, only 0.01% for *C. auris vs.* 0.1% for *C. glabrata* reference strain (by the way, these data underline an efficacy of povidone-iodine antiseptics also against *C. glabrata*).

Regarding the literature, there are only three studies that evaluated povidone-iodine against *C. auris in vitro*. Abdolrasouli *et al*. reported a growth inhibition for 12 clinical C. *auris* isolates by povidone-iodine concentrations between 0.07% and 1.25%, with a 3-min minimum contact time[9]. However, this study used a microdilution method that was not referred to any standard. In another study using a quantitative suspension test referring to the phase 2 application standards EN 13624:2013[7], Moore *et al*. reported that povidone-iodine suspension was effective against four isolates of *C. auris* after a 2-min contact time, but with a product concentration at 10%, largely higher than ours. Finally in the third study, Kean *et al*. investigated the activity of povidone-iodine on fungal biofilms of four *C. auris* isolates [10], using a three-dimensional complex model. Povidone-iodine concentrations of 1.25 to 2.5% were required to inhibit the biofilms after a 5-min contact time, while reduced sensitivity to clinically-relevant chlorhexidine concentrations was concomitantly reported[10]. Our study is the first one to evaluate the *in vitro* yeasticidal activity of three different iodine-based antiseptics against *C. auris*, according to the European Standard EN 1275:2005[8]. Our findings are in agreement with the few literature data available, suggesting that povidone-iodine based antiseptics express an excellent yeasticidal activity against *C. auris*, herein at much lower dilutions than the 80% recommended by the standard.

Some limitations can be underscored in our study. The *in vitro* behavior of the two fungal strains that have been tested appeared quite variable: in suspension and in culture, *C. albicans* and *C. auris* showed different characteristics from each other requiring minimal technical adaptations and some *C. auris* strains are known to exhibit differential phenotypes for aggregating and non-aggregating on which antiseptics could have different actions.

In conclusion, nosocomial transmission of *C. auris* appears to be multifactorial, involving a rapid and persistent skin colonization in affected patients that readily contaminate their immediate environment and the caregivers [2,5]. Controlling and preventing the spread of *C. auris* requires the isolation of any colonized/infected individual, the detection of contact cases, the detection of environmental contamination, but also the reinforcement of standard hygiene measures. Thus, disinfectants and antiseptics should have to play a critical role in such a context. The results of this study, carried out according to the technical recommendations of the EN 1275:2005 standard, support the use of commercial povidone-iodine products as antiseptics for the healthcare fighting against *C. auris*.

Table 1: logarithmic decimal reduction in *Candida auris* and *Candida albicans* viability after exposure to povidone-iodine-based antiseptics, according to the EN 1275:2005 standard

1 mL of *Candida* test suspension was added to 1 mL of water for injection, and then incubated for 2 minutes (min) at 20°C. Afterwards, 8 mL of each povidone-iodine-based solution were added at the desired concentration; this mixture was incubated for 15 min at 20°C. Thereafter, 1 mL of the resulting suspension was transferred to a tube containing 8 mL of sodium thiosulfate neutralizing solution and 1 mL of water for injection. After 5 min of neutralization at 20°C, aliquots of 1 mL of the aforementioned solution were plated (in duplicate) on malt extract media and incubated at 30°C for 48 h to subsequently enumerate the living yeasts by counting the CFU. Yeasticidal activity was expressed as the logarithmic decimal reduction in viability in comparison with the control situation without antiseptic.

	Betadine scrub®		Betadine dermique®		Betadine alcoolique®	
	4% (w/v) povidone-iodine		10% (w/v) povidone-iodine		5% (w/v) povidone-iodine	
	80%	0.25%	80%	0.1%	80%	2%
C auris 171 10744	> 4.2	> 4.2	> 4.2	< 2.7	> 4.2	> 4.2
C. albicans ATCC 10231	> 4.2	> 4.2	> 4.2	3.2	> 4.2	< 2.9

ACKNOWLEDGEMENTS

The authors thank the direction of the research of Tours hospital for its precious help.

ETHICS

No approval was necessary.

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