Demonstration of the yeasticidal efficacy of povidone-iodine–based commercial antiseptic solutions against *Candida auris*

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DISCLOSURE OF CONFLICT OF INTEREST

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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

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ETHICS

No approval was necessary.

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