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

3

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

25 DISCLOSURE OF CONFLICT OF INTEREST

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

27 ABSTRACT

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

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

37 Dear Editor,

38 First isolated from the external ear canal of a Japanese patient in 2009¹, *Candida auris* is an emerging yeast
39 pathogen that has been put in the spotlight over the last decade as a global health threat; this species has been
40 associated with multiple nosocomial outbreaks in several healthcare facilities worldwide, both in colonization
41 and invasive infection cases², and is sometimes challenging for its identification³ and for choosing the adequate
42 antifungal therapy because of elevated minimal inhibition concentrations (MICs)⁴. However, accurate data are
43 still lacking about *C. auris*, especially about its sensitivity to antiseptics that are usually supposed to play a
44 critical role in the fight against nosocomial transmission.

45 Chlorine-based surface disinfectants and improved hydrogen peroxide disinfectants were already demonstrated
46 to be highly active against *Candida* species, including *C. auris*^{6,7} (at the opposite of quaternary ammonium
47 disinfectants⁶), according to the European and International Standards EN 13624:2013 and ASTM E2197-11.
48 Nevertheless, no commercial disinfectant product has been officially registered so far by the health authorities
49 for specific use against *C. auris*. Data appear even more limited about the yeasticidal activity of antiseptics: only
50 a chlorhexidine-based product [chlorhexidine 2% (w/v) chlorhexidine gluconate in 70% (v/v)] and an iodine-
51 based antiseptic [10% (v/v) povidone-iodine] were shown effective so far, against *C. auris*, according to the
52 European Standard EN 13624:2013⁷. Thus, the aim of this study was to assess the *in vitro* yeasticidal activity of
53 three different iodine-based antiseptic products against *C. auris*.

54 The isolate of *C. auris*, number 171 10744, was obtained from a 58 year-old-Lebanese man who had been
55 hospitalized for liver transplantation³ (clinical collection of the Parasitology-Mycology laboratory of Tours
56 University Hospital, France). Species identification was confirmed by MALDI-TOF mass spectrometry and
57 DNA sequencing³. *C. auris* suspensions were obtained on malt extract media (PO 5055 A, OXOID, Hampshire,
58 UK)⁸, and prepared to yield a final organism density comprised between 1.5×10^7 and 5.0×10^7 colony-forming
59 units *per* milliliter (CFU/mL). The products to be tested included three commercial 'ready-to-use' povidone-
60 iodine-based antiseptics: one foaming solution for cutaneous application [4% (w/v) povidone-iodine; MEDA
61 PHARMA, Paris - France] named Betadine Scrub 4%[®] for preoperative hand washing or antiseptic washing,
62 and two solutions for cutaneous application [10% (w/v) povidone-iodine; MEDA PHARMA, Paris - France]
63 referred to as Betadine dermique 10%[®] used for the antiseptics of healthy or damaged skin and mucous
64 membranes, and [5% (w/v) povidone-iodine, in 70% (v/v) ethanol 96%; MEDA PHARMA, Paris - France] so
65 called Betadine alcoolique 5%[®] used for surgical or skin antiseptics before minor surgery. All the aforementioned
66 products were diluted with water for injection for the testing procedure: at 80% for all three, then at 0.25% for
67 Betadine Scrub 4%[®], at 0.10% for Betadine dermique 10%[®], and at 2% for Betadine alcoolique 5%[®]. The
68 method for evaluating the yeasticidal efficacy was based on a quantitative dilution-neutralization testing
69 according to the EN 1275:2005 standard⁸.

70 All the iodine-based antiseptics, at a concentration of 80% (as recommended by EN 1275:2005 standard⁸),
71 decreased *C. auris* viability to below the limit of efficiency defined for antiseptics⁸, achieving $>4 \text{ Log}_{10}$
72 reduction (Table 1). Yeastocidal concentrations were even largely lower for Betadine scrub[®] and alcoholic
73 Betadine alcoolique[®], at 0.25% and 2% respectively. Same kind of tests were carried out on the *Candida*
74 *albicans* ATCC 10231 reference strain and exhibited similar efficiency of the iodine-based antiseptics (Table 1).
75 As for *C. auris*, Betadine dermique[®] showed lower yeastocidal concentrations for *C. albicans* at 0.1%. In
76 addition, *C. glabrata* (*i.e.* a yeast species of clinical interest and which has proved problematic in surgical
77 intensive care departments) was also tested and actually found less susceptible to povidone-iodine antiseptics
78 than *C. auris*: for instance following 15 min contact with Betadine Scrub[®] diluted at 0.25%, the yeast survival
79 rate was only 0.07% for *C. auris* vs. 1.5% for *C. glabrata* ATCC MYA2950 reference strain, and 0.25% for the
80 clinical strains; for Betadine alcoolique[®], only 0.02% for *C. auris* vs. 1.8% for *C. glabrata* reference strain and
81 0.36% for the clinical strains; and eventually for Betadine dermique[®], only 0.01% for *C. auris* vs. 0.1% for *C.*
82 *glabrata* reference strain (by the way, these data underline an efficacy of povidone-iodine antiseptics also against
83 *C. glabrata*).

84 Regarding the literature, there are only three studies that evaluated povidone-iodine against *C. auris*
85 *in vitro*. Abdolrasouli *et al.* reported a growth inhibition for 12 clinical *C. auris* isolates by povidone-iodine
86 concentrations between 0.07% and 1.25%, with a 3-min minimum contact time⁹. However, this study used a
87 microdilution method that was not referred to any standard. In another study using a quantitative suspension test
88 referring to the phase 2 application standards EN 13624:2013⁷, Moore *et al.* reported that povidone-iodine
89 suspension was effective against four isolates of *C. auris* after a 2-min contact time, but with a product
90 concentration at 10%, largely higher than ours. Finally in the third study, Kean *et al.* investigated the activity of
91 povidone-iodine on fungal biofilms of four *C. auris* isolates¹⁰, using a three-dimensional complex model.
92 Povidone-iodine concentrations of 1.25 to 2.5% were required to inhibit the biofilms after a 5-min contact time,
93 while reduced sensitivity to clinically-relevant chlorhexidine concentrations was concomitantly reported¹⁰. Our
94 study is the first one to evaluate the *in vitro* yeastocidal activity of three different iodine-based antiseptics against
95 *C. auris*, according to the European Standard EN 1275:2005⁸. Our findings are in agreement with the few
96 literature data available, suggesting that povidone-iodine based antiseptics express an excellent yeastocidal
97 activity against *C. auris*, herein at much lower dilutions than the 80% recommended by the standard.

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

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

111

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

114 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
 115 mL of each povidone-iodine-based solution were added at the desired concentration; this mixture was incubated for 15 min at 20°C.
 116 Thereafter, 1 mL of the resulting suspension was transferred to a tube containing 8 mL of sodium thiosulfate neutralizing solution and 1 mL
 117 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
 118 malt extract media and incubated at 30°C for 48 h to subsequently enumerate the living yeasts by counting the CFU. Yeastocidal activity was
 119 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%
<i>C. auris</i> 171 10744	> 4.2	> 4.2	> 4.2	< 2.7	> 4.2	> 4.2
<i>C. albicans</i> ATCC 10231	> 4.2	> 4.2	> 4.2	3.2	> 4.2	< 2.9

120

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123 **ETHICS**

124 No approval was necessary.

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