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Letter to the Editor

Emergence of multidrug-resistant *Candida auris* in Taiwan

Sir,

Candida auris has been declared an emerging multidrug-resistant yeast and poses a great challenge in the field of infection control and prevention [1,2].

A 55-year-old man with a medical history of diabetes mellitus and pemphigus vulgaris underwent treatment with azathioprine (50 mg/day) and prednisolone (5 mg/day). Between 9 November 2017 and 30 December 2017 he was hospitalised at Chi Mei Medical Center (CMMC), located in Tainan City, Taiwan, due to pemphigus vulgaris-related skin and soft-tissue infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA), where he received anti-MRSA treatment. On 11 April 2018, several ruptured vesicles with erythematous changes and purulent discharge over the face were noted. The patient was a resident in Tainan City and did not have any overseas travel history prior to the hospital visit on 11 April 2018.

Bacterial cultures were obtained from the ruptured vesicles over the face and *Candida* sp. along with MRSA were recovered from trypticase soy agar plates supplemented with 5% sheep blood (Becton Dickinson & Co., Sparks, MD). Oral fluconazole (200 mg/day), in addition to minocycline, was prescribed for 14 days. Identification of the *Candida* sp. by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Biotyper MS; Bruker Daltonik GmbH, Bremen, Germany) from the growth on blood agar plates by the direct smear method yielded *C. auris* (score value, 1.857). Oral posaconazole (100 mg/day) was administered for 7 days. A follow-up fungal culture of the same facial lesion, performed at another hospital 1 month after the positive culture for *C. auris* at CMMC, did not grow any *Candida* spp.

The *Candida* isolate grown on the blood agar plate was identified as *Candida haemulonii* using Phoenix 100 YBC (Becton Dickinson & Co.) and VITEK®2 Yeast ID (bioMérieux, Marcy-l'Étoile, France) with a confidence value of 99.9% and probability 90%. Using the tube extraction method, Bruker Biotyper MS and VITEK® MS correctly identified the isolate grown on Sabouraud dextrose agar (SDA) (Becton Dickinson & Co.) as *C. auris* (score value, 2.049; confidence value, 99%). The *Candida* isolate did not grow on Mycosel™ Agar (Becton Dickinson & Co.), which is routinely used for primary isolation of fungi in the laboratory.

The internal transcribed spacer (ITS) region of the ribosomal RNA (rRNA) subunit for the *Candida* isolate was amplified and sequenced using the primers ITS-1 and ITS-4 and showed 99% homology with *C. auris* in GenBank (accession no. **KY656976.1**) [3]. Sequencing analysis of the D1–D2 domain of the 26S rRNA gene of the *Candida* isolate revealed that the sequence was identical (100% identity) to *C. auris* (accession no. **MH793528.1**).

Susceptibility of the isolate to nine antifungal agents was determined using two commercial systems, namely VITEK®2 Antifungal Susceptibility System (AST-YS08 card; bioMérieux) and Sensititre® YeastOne® system (Trek Diagnostic Systems Ltd., East Grinstead, UK). Minimum inhibitory concentrations (MICs) of fluconazole were also determined using the broth microdilution (BMD) method as recommended by the Clinical and Laboratory Standards Institute (CLSI) [4]. Because there are currently no MIC breakpoints recommended by the CLSI for *C. auris* isolates [4], the MICs of the isolate were interpreted according to the MIC breakpoints suggested by the US Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/fungal/candida-auris/recommendations.html) and Farmakiotis and Kontoyiannis (Table 1) [5]. High MICs of fluconazole (8–16 mg/L) and amphotericin B (2–8 mg/L) were noted using the two commercial susceptibility testing systems. Using the CLSI BMD method, an MIC of 16 mg/L was determined for fluconazole (Table 1). The antifungal susceptibility findings were consistent with previous studies [1,2]. Importantly, in contrast to the Taiwanese isolate, *C. auris* isolates with very high fluconazole and voriconazole MICs but low amphotericin B MIC have been reported [1,2]. Data from the UK indicated that previous exposure to fluconazole was a significant risk factor for *C. auris* colonisation and/or infection [2]. The patient in the current study did not have previous exposure to fluconazole prior to acquisition of *C. auris*.

Discrepant MIC results for caspofungin by VITEK®2 (0.25 mg/L) and Sensititre® YeastOne® (8 mg/L) against the micafungin-susceptible *C. auris* isolate were found (Table 1). The *C. auris* isolate had wild-type *FKS1* as determined by *FKS1* sequencing [6]. An Eagle effect (or the paradoxical growth effect) exhibited in the *C. auris FKS1* wild-type isolate described by Kordalewska et al. might explain this phenomenon [6]. The current findings also support that routine in vitro testing of *C. auris* isolates for susceptibility to caspofungin by the BMD method should be avoided [6].

Surveillance cultures using SDA of the patient's and environmental swab samples, including those from the desktop, door handle, dressing cart and chairs of the outpatient clinic where the patient visited 1 month after the notification of *C. auris* isolation, were all negative for *Candida* spp.

Because the *C. auris* isolate was unable to grow on Mycosel™ Agar containing cycloheximide (400 mg/L), the MICs to cycloheximide of 34 *Candida* isolates, including 31 bloodstream isolates, the *C. auris* isolate and 2 recommended quality control strains, were determined using the BMD method [4]. Apart from five *Candida albicans* isolates, all other *Candida* isolates tested were inhibited by cycloheximide at 64 mg/L. The MIC of *C. auris* to cycloheximide was low (1 mg/L) (Table 1). Based on this finding, in addition to chlorine-based products that are currently recommended in the control of *C. auris*, cycloheximide-based products may be useful disinfectants in the future.

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Table 1
Antifungal susceptibility of the *Candida auris* isolate using two commercially available systems and the broth microdilution (BMD) method.

Antifungal agent	VITEK®2		Sensititre® YeastOne®		BMD[b]	
	MIC range (mg/L)	Interpretation[a]	MIC range (mg/L)	Interpretation[a]	MIC range (mg/L)	Interpretation[a]
Fluconazole[d]	8	S	16	S	16	S
Voriconazole[e]	≤0.12	S	0.06–0.12	S	ND	–[c]
Itraconazole[f]	–	–	0.25	–	ND	–
Posaconazole[f]	–	–	0.06	–	ND	–
Caspofungin[d]	0.25	S	8	R	ND	–
Micafungin[d]	≤0.06	S	0.25–0.5	S	ND	–
Anidulafungin[d]	–	–	0.5–1	S	ND	–
Flucytosine[e]	≤1	S	0.06–0.12	S	ND	–
Amphotericin B[d]	4–8	R	2–4	R	ND	–
Cycloheximide[g]	–	–	–	–	1	–

MIC, minimum inhibitory concentration; S, susceptible; R, resistant; ND, not done; CDC, US Centers for Disease Control and Prevention.
[a] MICs were determined twice and were interpreted according to the breakpoints suggested by the CDC (https://www.cdc.gov/fungal/candida-auris/recommendations.html) and Farmakiotis and Kontoyiannis [5].
[b] BMD method as recommended by the Clinical and Laboratory Standards Institute (CLSI) [4].
[c] –, indicates not available.
[d] MIC breakpoints for defining *C. auris* isolates as resistant to antifungal agents recommended by the CDC are as follows: fluconazole, ≥32 mg/L; caspofungin, ≥2 mg/L; micafungin, ≥4 mg/L; anidulafungin, ≥4 mg/L; amphotericin B, ≥2 mg/L.
[e] MIC breakpoints for defining *C. auris* isolates as resistant to voriconazole (≥2 mg/L) and flucytosine (≥128 mg/L) recommended by Farmakiotis and Kontoyiannis were used [5].
[f] MIC breakpoints for defining *C. auris* isolates as resistant to posaconazole and itraconazole are not available from the CDC or Farmakiotis and Kontoyiannis [5].
[g] MICs to cycloheximide of 34 *Candida* isolates, including 31 bloodstream isolates, the *C. auris* isolate (above) and 2 recommended quality control strains, were determined using the BMD method. For *Candida parapsilosis* ATCC 22019 and *Candida krusei* ATCC 6258, cycloheximide MICs were 8 mg/L and 0.25 mg/L, respectively. For other *Candida* spp. tested, MIC ranges were >512 mg/L for *C. albicans* ($n=5$), 4–8 mg/L for *C. parapsilosis* ($n=5$), 2–4 mg/L for *C. tropicalis* ($n=5$), 1 mg/L for *C. glabrata* ($n=5$), 0.25–1 mg/L for *C. krusei* ($n=5$), 0.5–1 mg/L for *C. lusitaniae* ($n=4$), 32 mg/L for *C. haemulonii* ($n=1$) and 64 mg/L for *C. catenulata* ($n=1$).

The source of *C. auris* in this patient remains unclear. He did not have any overseas travel history. He only had healthcare exposure at the hospital, including one hospitalisation 6 months previously, and had visited the outpatient clinic several times. Persistence of skin colonisation lasting 1–3 months as well as environmental contamination lasting 2–3 months have been described previously [1,2]. However, the surveillance cultures of the patient and environmental swabs from the outpatient clinic visited by the patient were negative for *C. auris*.

In conclusion, here we present the first clinical isolate of *C. auris* in Taiwan and demonstrate the potent activity of cycloheximide against this organism.

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Competing interests

None declared.

Ethical approval

Not required.

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Hung-Jen Tang
Department of Medicine, Chi Mei Medical Center, Taiwan
Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan

Chih-Cheng Lai
Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Taiwan

Feng-Jie Lai
Department of Dermatology, Chi Mei Medical Center, Taiwan

Shu-Ying Li
Center for Diagnostics and Vaccine Development, Centers for Disease Control, Taiwan

Hui-Yun Liang
Infection Control Center, Chi Mei Medical Center, Taiwan

Po-Ren Hsueh*
Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

*Corresponding author. Tel.: +886 2 2312 3456 × 65355, fax: +886 2 2322 4263.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh)

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