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Case Report: Emergence of *Candida auris* in the Indian Ocean Region

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Abstract. *Candida auris* is an emerging multidrug-resistant yeast that can cause severe infections and spread easily between hospitalized patients, leading to outbreaks in hospital. Here, we report the first four cases of colonization and invasive infection with *C. auris* reported in the Indian Ocean region. All cases were observed in the French overseas Reunion Island, a very popular destination for European travelers. Three patients had urinary tract or skin colonization, and one had a fatal invasive infection. In three cases, including that of the infected patient, the yeast was not initially identified as *C. auris*, preventing specific hygiene measures to be implemented as suggested in the December 2016 clinical alert to European healthcare facilities. The infected patient likely acquired *C. auris* in the intensive care unit from the first colonized patient. This is the first case of *C. auris* infection and the first potential case of nosocomial transmission of the pathogen to be reported in the French overseas Reunion Island.

INTRODUCTION

The emerging pathogen *Candida auris* is now considered a threat to global health.¹ *Candida auris* is a multidrug-resistant yeast, as most strains are resistant to fluconazole^{2,3} and have a reduced susceptibility to other triazole antifungals.⁴ Given the high rates of treatment failure and mortality associated with invasive infections, *C. auris* is currently being considered as a highly resistant pathogen.^{5–9} Moreover, the risk of epidemic is high because of *C. auris*'s persistence in the environment and resistance to common disinfectants.¹⁰

In the Indian Ocean region, the prevalence of *C. auris* is unknown because no cases of colonization or infection have been reported to date. Yet given its geographical location, with India to the north and South Africa to the west, the Indian Ocean region is at high risk for the spread of this pathogen. It is also an important tourist destination, notably for Europeans, raising fears that it might help propagate *C. auris* to countries of the north (Figure 1).

Here, we report all cases of *C. auris* observed in Reunion Island to date. We also checked the literature on *C. auris* in the Indian Ocean region.

METHODS

French guidelines recommend systematic screening for multidrug-resistant bacterial carriage on hospital admission in patients who have traveled in the past 12 months and on intensive care unit (ICU) admission in all patients whether or not they have spent time abroad. Thus, since 2010, all clinical samples growing yeasts collected in our ICU were routinely screened for *C. auris*. In addition, we retrospectively reviewed all cases of infection by *C. auris* identified in the laboratory and retrospectively reanalyzed all isolates of *Candida* sp. that have been stored and not identified to the species level before the

recommendations issued in 2018 to even identify colonizing yeasts.¹¹

Candida species were identified using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry and MALDI Biotyper IVD[®] database. All isolates identified as *C. auris* and responsible for colonization or infection were then stored and sent to the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA, Institut Pasteur, Paris, France), for confirmation of identification. The minimal inhibitory concentrations (MICs) were determined by the European Committee on Antimicrobial Susceptibility Testing method.¹² Short tandem repeat (STR) typing assay was used to determine geographic clade of the isolates.¹³

CASES (TABLE 1)

Four patients were colonized or infected with *C. auris* between 2010 and 2019. All patients were hospitalized in the same ICU. Informed consent to publish was obtained from cases 1, 3, and 4 and from the family of the dead case 2.

Case 1. A 76-year-old woman, who had spent 6 weeks in Mauritius for holidays, was admitted to the ICU in 2015. Her past medical history included untreated chronic lymphocytic leukemia and chronic heart failure. In Mauritius, she was hospitalized in the ICU for 1 month for dyspnea. A broad-spectrum antibiotic regimen of meropenem and levofloxacin was initiated. Her clinical condition deteriorated, prompting her medical transfer to the ICU of Reunion Island where she was diagnosed with *Legionella pneumophila*. New infectious complications required urine culture, which grew *Candida* species later (in 2019), identified as *C. auris* but not stored. The patient was considered to be colonized in the urinary tract, and no antifungal susceptibility testing was performed, and no antifungal drug was prescribed. The patient was discharged from the ICU on day 49.

Case 2. In April 2015, a 36-year-old man with paroxysmal nocturnal hemoglobinuria treated with eculizumab was admitted to the ICU for coma due to cerebral thrombophlebitis with intracranial hypertension. No travel history was reported. The patient was diagnosed with *C. auris* fungemia (positive

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FIGURE 1. Indian Ocean region: Reunion Island is directly connected to European continent via several daily flights to Paris. White dotted line showed Reunion Island's daily flights.

blood and central venous catheter cultures). Caspofungin was prescribed for a period of 13 days (loading dose of 70 mg, followed by 50 mg/day). The persistence of positive blood cultures prompted the addition of liposomal amphotericin B (350 mg/day), after 5 days of caspofungin monotherapy. The diagnosis of *C. auris* endocarditis was made based on the discovery of vegetation of the mitral valve by transoesophageal echocardiography and the persistence of positive blood cultures until the patient died on day 19 from refractory intracranial hypertension. The species was confirmed at the National reference center for invasive mycoses and antifungals (NRCMA) (#Centre National de Référence des Mycoses Invasives et Antifongiques [CNRMA] 15.337). The isolate exhibiting high fluconazole MIC (> 64 mg/L) was found to belong to the Indian clade I.

Case 3. In 2016, a 30-year-old man with no recent travel and no past medical history apart from chronic alcohol abuse was admitted to the ICU for pneumonia due to *L. pneumophila*. Hospitalization was complicated by multiple nosocomial infections, which required successive treatments. On day 30, *Candida* sp., later (in 2019) identified as *C. auris*, was recovered from the patient's skin but neglected. The patient was discharged from the ICU on day 54 and from hospital on day 100.

Case 4. In 2019, an 83-year-old man who had traveled in Saudi Arabia and India for 1 month was admitted to an Indian ICU for septic shock due to pneumonia. The patient, who had no past medical history, was treated with a broad-spectrum antibiotic regimen of penicillin, meropenem, and minocycline. He was discharged from the Indian ICU after 2 weeks. He returned home to Reunion Island, and 3 weeks later, he was readmitted to the ICU for necrotizing pleuropneumonia of the right lobe with septic shock. Bronchoalveolar lavage fluid and

blood cultures revealed the presence of carbapenem-resistant *Klebsiella pneumoniae*. Vancomycin-resistant *Enterococcus faecium* was detected via rectal swab. Urine culture grew yeast identified as *C. auris* with no other positive body sites. The patient's condition improved rapidly under antibiotics therapy, but no antifungal drug was prescribed. He was discharged from the ICU on day 2 and from hospital on day 10. The *C. auris* isolate was sent to the NRCMA (#CNRMA19.95) where the species was confirmed. The isolate also belonged to Indian clade I, and antifungal susceptibility testing showed high fluconazole and flucytosine MICs (MICs > 64 mg/L).

LITERATURE REVIEW AND DISCUSSION

These cases suggest that *C. auris* has been present in the Indian Ocean region for at least 5 years. As in other reports, *C. auris* was here found mainly in immunocompromised ICU patients as a skin or urinary tract colonization.^{4,14}

In the literature, most cases reported of *C. auris* colonization and infection concern the Indian subcontinent.^{4,14} Patients hospitalized in Indian hospitals are at very high risk of *C. auris* colonization or infection because *C. auris* was recovered in the majority of ICUs (19/27) studied in India where it represents 5.2% of all *Candida* spp. isolates.¹⁵ Most cases of *C. auris* invasive infection occur in critically ill patients with major risk factors¹⁴ and are associated with a mortality rate above 50%.¹

Before our study, no case of *C. auris* had been documented in the Indian Ocean region. The four cases reported here were all observed in Reunion Island. Two of the cases occurred after a stay in India (Case 4) and Mauritius (Case 1). Case 3 remains

TABLE 1
Characteristics of cases and risk factors for *Candida auris* invasive infection

Case	1	2	3	4
Year/month	2015/April	2015/April	2016/May	2019/June
Gender, age (years)	Female, 76	Male, 36	Male, 30	Male, 83
Comorbidity	Chronic lymphocytic leukemia and chronic heart failure	Hypertension	None	None
Country visited in the previous year	Mauritius	None	None	India and Saudi Arabia
Recent intake of broad-spectrum antibiotics	Yes	No	Yes	Yes
Total parenteral nutrition	No	No	No	No
Urinary catheterization	Yes	Yes	Yes	Yes
Postoperative drain placement	No	No	No	No
Vascular surgery	No	No	No	No
Type of disease or location of isolate	Colonization (urinary tract)	Candidemia and central venous catheter tip	Colonization (skin)	Colonization (urinary tract)
Other <i>Candida</i> species	<i>C. tropicalis</i>	No	<i>Candida albicans</i>	<i>Candida parapsilosis</i>
Antifungal resistance	Not available	Fluconazole 5-Flucytosine	Not available	Fluconazole 5-Flucytosine Voriconazole
Treatment	0	Echinocandin 13 days	0	0
Death	No	Yes	No	No

C. tropicalis = *Candida tropicalis*.

unexplained in terms of the origin of contamination, except for a stay in an ICU. However, no other patient staying at the same time was retrospectively identified as a carrier of the yeast or having recently traveled to a country at risk for *C. auris* contamination.

As often reported, both isolates tested exhibited high fluconazole and flucytosine MICs in line with recent studies published.^{16,17} Susceptibility to echinocandins and amphotericin B was considered normal (Table 2). Interestingly, the three 5-flucytosine-resistant *C. auris* isolates (6%) analyzed by Lockhart et al. all came from India, which is also the case for the French isolates including ours (for Case 4), both belonging to the Indian clade.^{16,18} Moreover, both isolates (Case 2 and Case 4) have the same genotype (STR genotype 17) which is the main genotype observed in the South Asian clade I (Table 3).¹³

A first clinical alert on the emergence and spread of *C. auris* was issued in 2016 by the CDC.¹⁹ In March 2018, the French network of Hospital Infection Control Committees also published a clinical alert,¹¹ prompting the implementation of specific hygiene measures for the prevention of *C. auris* transmission. After national alert,¹¹ all patients admitted in our ICU were screened (i.e., rectal swab) for *C. auris* and for multidrug-resistant pathogens. All screen-positive patients were isolated, and specific measures of hygiene were set up. The following measures were recommended: all patients colonized or infected with *C. auris* must be isolated in a single room; standard precautions including hand hygiene must strictly adhered to (handwash with soap and water to remove visible soiling followed by alcohol hand rub during care

activities, and alcohol hand rub in the absence of visible soiling between care activities); and the bed space and/or room of colonized or infected patients must be terminally cleaned after discharge using a hypochlorite at 1,000 ppm of available chlorine (i.e., a concentration higher than that routinely used). Non-environmental screening of healthcare workers was carried out, but all close contacts (patients in the same ICU) were screened and isolated until three consecutive negative screens were obtained (at least 24 hours apart). Before these recommendations, the ICU was disinfected with a product composed of quaternary ammonium compounds unable to eradicate *C. auris*.^{20,21} We hypothesized that Case 2 was contaminated via the environment on the grounds that he was diagnosed before the implementation of specific hygiene measures and was hospitalized in the same ICU room as Case 1, but after Case 1 left (4 days later). The strain from Case 1 being unavailable for analysis, we tested this hypothesis by retrospectively comparing five spectra obtained from the two patients suspected of cross-transmission with MALDI-TOF mass spectroscopy (Bruker Daltonics, Bremen, Germany). Two spectra from Case 1 were added to the MALDI Biotyper IVD database (Bruker Daltonics) to create a new main spectrum profile. Three spectra from Case 2 were then compared with the new database. In each instance, the two spectra from Case 1 matched the first two positions of the top 10 ranking with a log-score value > 2.0 (Figure 2). Although the discriminating power of MALDI-TOF to finely type bacteria or yeasts is limited, it is now recognized that the mass spectrometry is also able of strain typing and notably to classify with a good reliability the

TABLE 2
Antifungal resistance of *Candida auris* isolates (Cases 2 and 4)

Isolate	Antifungal (minimal inhibitory concentration mg/L)						
	Fluconazole	Voriconazole	Posaconazole	Amphotericin B	5-Flucytosine	Caspofungin	Micafungin
CNRMA* 15.337 (Case 2)	≥ 64	0.125	≤ 0.014	0.25	≥ 64	0.015	0.03
CNRMA* 19.95 (Case 4)	≥ 64	1	0.06	0.125	≥ 64	0.03	0.03

Boldface indicates a resistance to two antifungal classes which are traditionally used in intensive care unit.

* CNRMA: French National Reference Center for Invasive Mycoses and Antifungals (Pasteur Institute, Paris). Boldface indicates a significant result.

TABLE 3
Short tandem repeat genotype profile for isolates of Cases 2 and 4

Isolate	STR genotype	Locus											
		M2a	M2b	M2c	M3-1a	M3-1b	M3-1c	M3-1la	M3-1lb	M3-1lc	M9a	M9b	M9c
Case 2	17	66	19	9	30	10	18	36	29	22	18	11	9
Case 4	17	66	19	9	30	10	18	36	29	22	18	11	9

STR = short tandem repeat. The number of tandem repeats is indicated for each marker.

microorganisms in clonal complexes such as ST (sequence type) for bacteria.^{22–24} This typing method is based on specific protein peaks. Thus, the strains of the Cases 1 and 2 are closer together than the other *C. auris* spectra in the Bruker mass spectrometer database. This finding supported the hypothesis of nosocomial transmission from Case 1 to Case 2. Accordingly, Case 2 was retrospectively reported to the health authorities, as the first potential case of nosocomial transmission documented in France. It should be noted, however, that this transmission cannot be confirmed by a molecular typing method because the *C. auris* strain isolated from Case 1 in 2015 is no longer available.

Unsurprisingly, *C. auris* has been present in the Indian Ocean area for several years. Thanks to its central location in Indian Ocean and thanks to its technical platform, Reunion Island supports the surveillance and control actions of *C. auris* that were already implemented on the island as a result of these cases.

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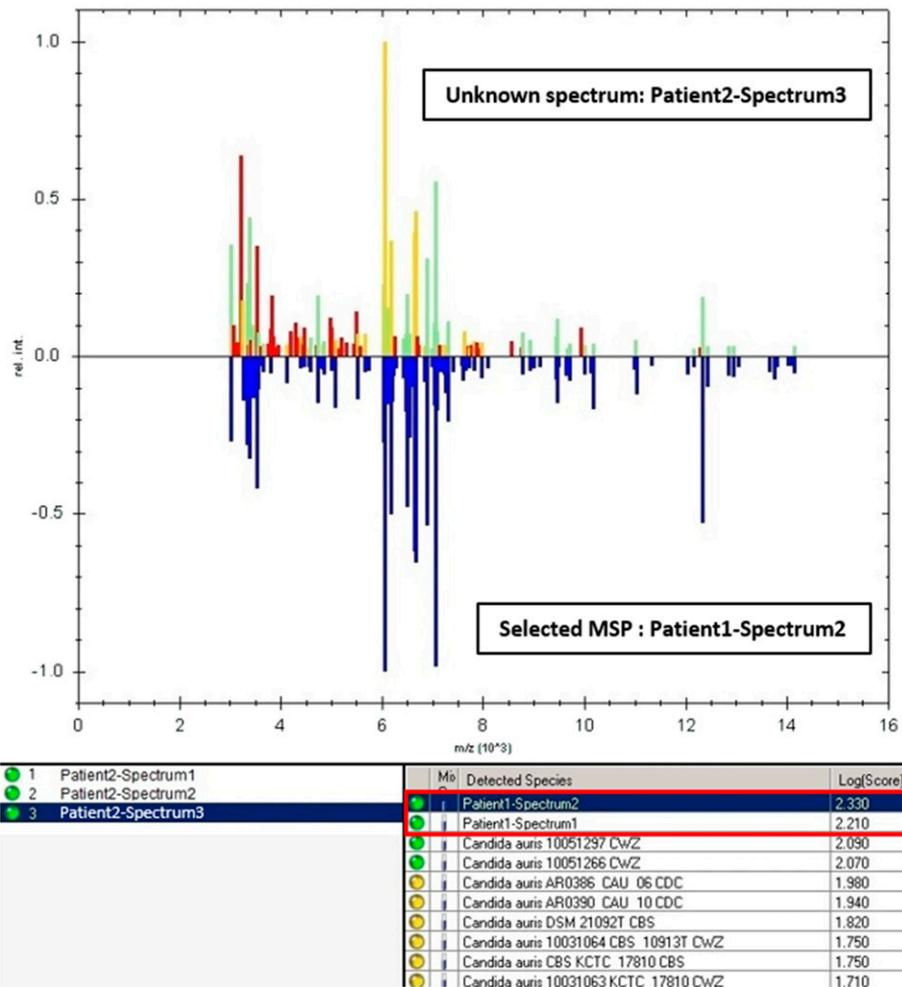


FIGURE 2. Comparison of a spectrum from Case 2 (Spectrum 3) to the modified Bruker database (MALDI Biotyper IVD database version 2.3 7712. Main spectrum profile modified with the addition of two spectra from Case 1 for a total of 11 *Candida auris* spectra). The spectra of Case 1 matched the first two positions (log-score values: 2.33 and 2.210) of the top 10 ranking. Our tested spectrum (or unknown spectrum) is represented in the upper part of each panel, and the reference spectrum selected from the database appears in blue in the lower part of each panel (thresholds of composite correlation index: < 0.80, red: low matching; 0.80–0.90, yellow: moderate matching; > 0.90, green: high matching). This figure appears in color at www.ajtmh.org.

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