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Review Article

Candida auris: A pathogen difficult to identify, treat, and eradicate and its characteristics in Japanese strains

S. Iguchi, Y. Itakura, A. Yoshida, K. Kamada, R. Mizushima, Y. Arai, Y. Uzawa, K. Kikuchi*

Department of Infectious Diseases, Tokyo Women's Medical University, Tokyo, Japan

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ABSTRACT

Candida auris is a multidrug-resistant and emergent pathogen that has caused healthcare-associated infection outbreaks. Recently, *C. auris* has spread worldwide; nevertheless, it was unexpectedly rare before 2009. Based on the molecular epidemiological analysis, *C. auris* may independently emerge at specific areas at first and recently may be transmitted to other continents. As *C. auris* cannot be detected using conventional methods, internally transcribed spacers, D1/D2 regions of the 26S rDNA sequencing, and/or matrix-assisted laser desorption ionization time-of-flight mass spectrometry method can be selected as comparatively accessible choices. Thus, detection of *C. auris* using the conventional method might be underestimated. In Japan, all *C. auris* strains were isolated from ear specimen and not from invasive mycoses. Japan strains were classified as an East Asian clade under a single clone. Although colonization, virulence, and infection pattern are almost the same as with other *Candida* species, its antifungal resistance is different. Fluconazole resistance is notably common, but resistance to all three classes of antifungals (azole, polyene, and echinocandin) rarely exists. Once *C. auris* is detected, screening, emphasis on hand hygiene adherence, use of single-patient room isolation, contact precaution, surveillance, and eradication from the environment and patients are appropriately required for infection control.

Contents

1. Introduction

Candida auris was first identified from an external ear canal discharge in 2009 in Japan [1]. "Auris" is the Latin term for ear. After

* Corresponding author. Department of Infectious Diseases, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan.
E-mail addresses: iguchi.shigekazu@twmu.ac.jp (S. Iguchi), kikuchi.ken@twmu.ac.jp (K. Kikuchi).

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a long blank period in Japan, the second case of *C. auris* was detected in 2017 [2], and further five strains in 2018 [3]. All strains originated from otorrhea. During the Japanese blank period, many *C. auris* strains were identified globally, and only a few infection and/or outbreak cases were reported.

C. auris has three important characteristics: frequent misidentification as under-recognition, resistance to multi-antifungals, and maintenance of easy colonization to the human body and environment. For these reasons, if infection cases and/or outbreaks occur, controlling the situations will be extremely difficult. Therefore, this emerging pathogen should be sufficiently understood.

2. Epidemiology

The reported cases of *C. auris* were 620 (bloodstream infection, 110; other infections, 40; colonization, 466; and unknown, 4) in Europe [4] and 463 in the USA (based on cultures from specimens collected during the course of clinical care to diagnose or treat the disease, confirmed, 433; probable, 30) [5]; in addition, *C. auris* cases are identified from all five continents. However, *C. auris* was rarely reported before 2009. It is unexpected that only four out of 15,271 strains including the SENTRY program (2004–2015) were detected [6]. Transmission among patients and deep-seated *C. auris* mycosis occurred at a number of countries in the last 10 years [7]. *C. auris* was isolated from Japan [1,2], Pakistan [6], India [13], South Africa [9], Venezuela [8], Israel [21], Colombia [22], Korea [23], Kuwait [24], USA [5], UK [25], Malaysia [26], Brazil [27], Oman [28], Panama [29], China [30], United Arab Emirates [31], Iran [61], Switzerland [32], Spain [4], Germany [4], France [4], Belgium [4], Norway [4], Canada [33], and Australia [60] (Fig. 1). On the single nucleotide polymorphism (SNP) analyses using the next-generation sequencing, global *C. auris* strains are divided into the following four clades: East Asia, South Asia, South Africa, and South America [3,6]. Based on this fact, *C. auris* independently supposedly emerged in each area at first. Recently, *C. auris* strains distinguished by multiple clades were detected in US and UK outbreak cases [38,58,59] and an otomycosis case (no travel history) in Iran [61]; therefore, these *C. auris* strains may be transmitted over continents.

C. auris is becoming a very well-known pathogen; it was reported as the 6th most common pathogen of bloodstream infection in a Venezuelan hospital [8], 0.3% prevalence rate of *C. auris* fungemia in the South African hospital network [9], and 5th most common pathogen (prevalence rate, 5.3%) of candidemia in Indian intensive care units (ICUs; detection in 19 of 27 ICUs) [10].

The true prevalence rate of *C. auris* colonization and mycoses remains unknown. The bottom factor is the absence of accurate identification system according to the biochemical characteristics [11]. Currently, some accurate diagnostic methods such as polymerase chain reaction (PCR), mass spectrometry, loop-mediated isothermal amplification (LAMP), and T2 magnetic resonance exist, but they are not used routinely because of labor, cost, and/or absence of equipment.

3. Phenotypic characteristics

C. auris is closely related to *C. krusei*, *C. haemulonii*, and *C. lusitaniae* phylogenetically [6]. It is characterized as white to cream colonies with a smooth edge on the Sabouraud-dextrose agar and pink colonies on CHROMagar *Candida* medium [12] (Fig. 2.). *C. auris* grows well at 38 °C or 42 °C and is assimilated with *N*-acetyl glucosamine, succinate, and gluconate in spite of its close relationship with *C. haemulonii* and *C. duobushaemulonii* [12]. Surprisingly, Japanese and Korean reference isolates are not assimilated with *N*-acetyl glucosamine [13].

4. Identification method

C. auris can be misidentified in the conventional biochemical kit, such as Vitek 2 YST (bioMérieux, Inc.), API 20C (bioMérieux, Inc.), BD Phoenix yeast identification system (Becton, Dickinson and Company), MicroScan (Beckman Coulter, Inc.), and RapID Yeast Plus (Remel, Inc.) (Table 1) [14]. Initially, identification is not commonly

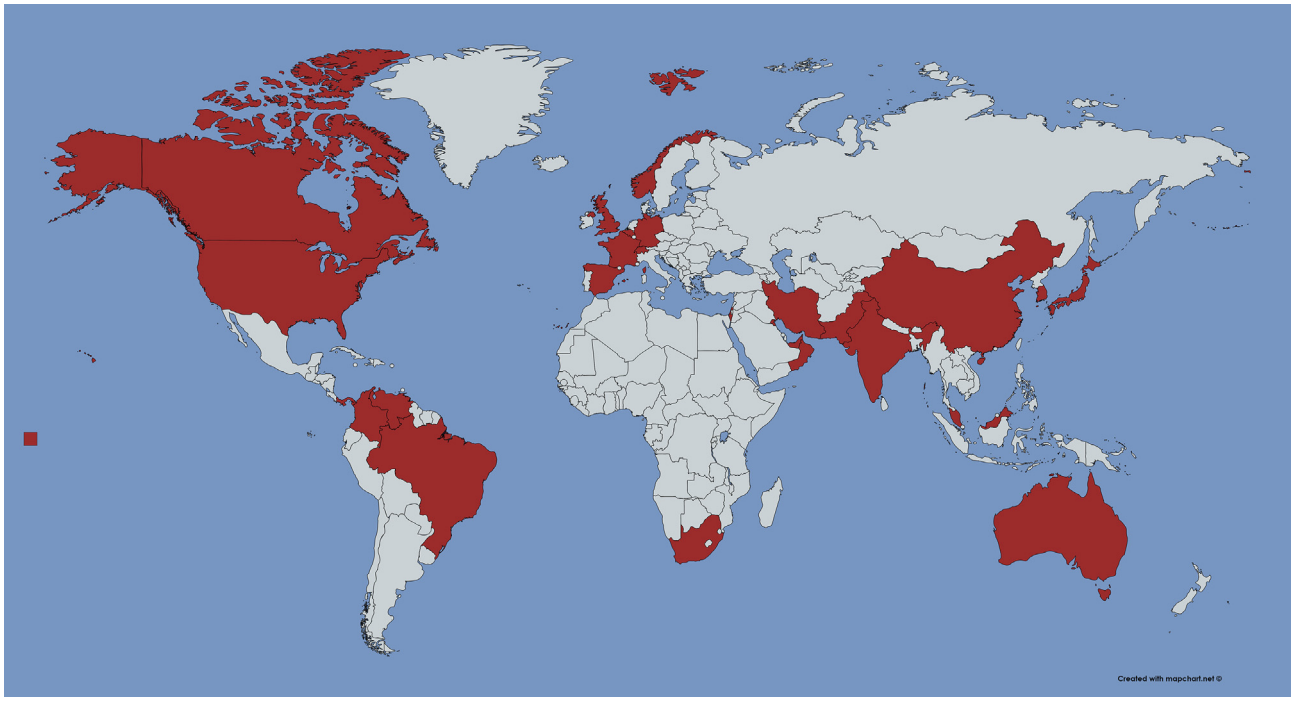

Fig. 1. Countries reported with *Candida auris*.

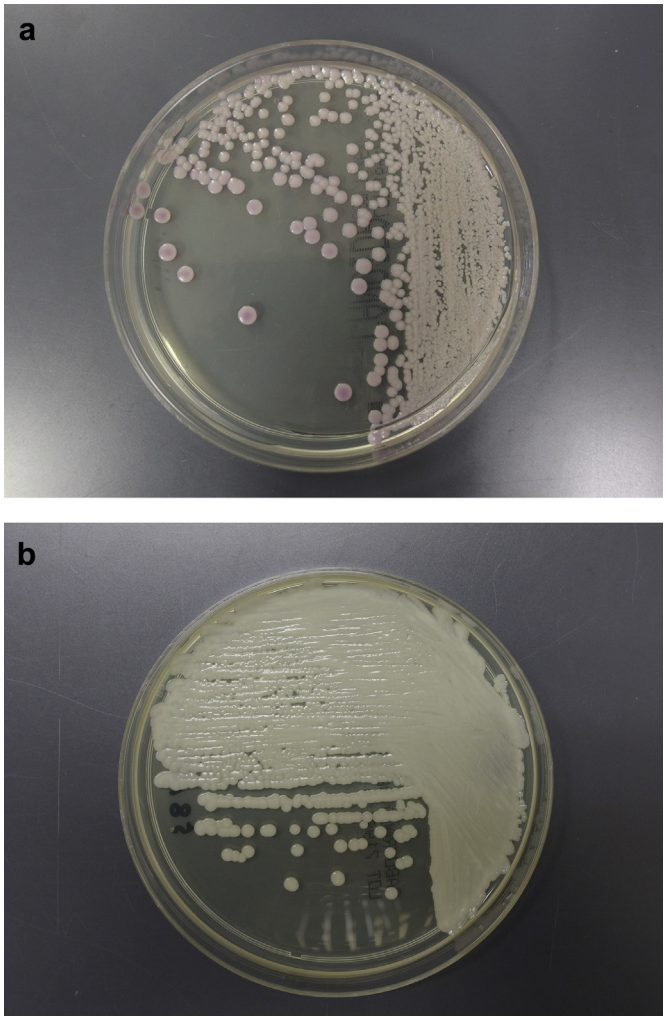

Fig. 2. *Candida auris* colonies on CHROMagar *Candida* at 35 °C at 72 h (a) and Sabouraud agar at 35 °C at 72 h (b).

performed in cases suspected with contamination. Therefore, the following four situations are suggested to require *C. auris* identification: (1) misidentification pattern on conventional method (Table 1), (2) one or more antifungal class resistances, (3) detection at the hospital or other clinical units, and (4) patients from high prevalence area or country.

Table 1
Misidentification of *C. auris* [14].

Identification method	Misidentified as
Vitek 2 YST	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* (characteristic red color not present) *Candida sake*
API ID32C[a]	*Candida sake* *Saccharomyces kluyveri*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata*
MicroScan	*Candida famata* *Candida guilliermondii* *Candida lusitaniae* *Candida parapsilosis*
RapID Yeast Plus	*Candida parapsilosis*

[a] Our experience.

PCR and mass spectrometry can identify *C. auris* identification more accurately than biochemical reactions. The PCR method is performed by extracting DNA, amplifying and sequencing the internal transcribed spacers and D1/D2 regions of the 26S rDNA, and clustering by Basic Local Alignment Search Tool (BLAST) [15]. Mass spectrometry method is used for matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Currently, the Bruker Biotyper and Vitek MS brands can be used for *C. auris* identification. *C. auris* can be identified using the Vitek MS brand if the database is Saramis Ver. 4.14 or later [14]. In other words, whether the database includes *C. auris* or not remains critically important.

Remarkably, some new identifying methods are reported. As the incubation method to classify *C. haemulonii* complex, the CHROMagar *Candida* medium supplemented with Pal's agar can be used [16]. *C. auris* grows as white to cream smooth colonies on this medium at 37°C-42 °C after 24–48 h, whereas *C. haemulonii* complex grows as light pink smooth colonies after 24–48 h and cannot grow at 42 °C [16]. CHROMagar Candida medium with Pal's agar is made by a 1:1 mixing ratio. Pal's agar preparing method is compounding 50 g unsalted powdered sunflower seeds to 1 L of distilled water, boiling for 30 min, filtering, supplementing with creatinine 1 g + glucose 1 g + KH_2PO_4 1 g, adjusting pH to 5.5, and adding agar of 15 g/L [17].

Yamamoto et al. developed a new identification method using LAMP as a simpler approach. Targeting 869 bp DNA fragment is encoded a pyruvate: ferredoxin oxidoreductase domain [18].

C. auris detection method using T2 magnetic resonance (T2MR; T2 Biosystems, Inc.) technology was also reported. This study used 89 clinical samples (*C. auris* culture positive 46, negative 43), with sensitivity of 0.89 (95% confidence interval [CI]: 0.888–0.894), specificity of 0.98 (95% CI: 0.975–0.978), positive predictive value of 0.98 (95% CI: 0.975–0.978), and negative predictive value of 0.89 (95% CI: 0.891–0.896) [19]. These results are almost similar (sensitivity 91.1%, specificity 99.4%) to those of other *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) [20].

5. Infection

C. auris is often isolated from the blood, urine, sputum, ear discharge, cerebrospinal fluid, and soft tissue. Discrimination between colonization and infection is difficult, except in the blood. The mortality rate of *C. auris* fungemia reached to 30%–60% [34], which is probably high to that of the general candidemia (25%) [35]. According to a systematic review on *C. auris*, the global crude mortality rate is 29.75% (94/316) [36].

Generally, *C. auris* colonization or infection risk factor is thought to be similar to that of other *Candida* species, such as urinary or central venous catheter placement, intravenous hyperalimentation, antibiotics administration, after the surgery, and ICU admission [37].

In a subgroup analysis of a prospective candidemia case study in India, *C. auris* cases have longer ICU stay and are associated with hospital characteristics (north Indian, public sector), with respiratory illness, vascular surgery, antifungal administration, and low Acute Physiology and Chronic Health Evaluation (APACHE) II score [10].

In another study of *C. auris* outbreak in the UK neuro-ICU, long ICU stay, using reusable axillary temperature probe, and systemic fluconazole administration were found as risk factors of colonization or infection [38]. A multivariate analysis in China identified diarrhea and tetracycline use as risk factors [39].

In a lung transplantation situation, *C. auris* transmitted from the donor to the recipient's respiratory tract was reported in the USA [40], which is as expected.

Table 2
Antifungals provisional breakpoint and resistance rate (RR) of *C. auris*.

	μg/mL [6,14]	RR (%) [36]	RR (%) in Japan (see Table 3)
Fluconazole	32	44.3	15.4
Voriconazole	2	12.7	7.7
Micafungin	4	1.3	0
Caspofungin	2	3.5	0[a]
Amphotericin B	2	15.5	0
Flucytosine	128	2.0	0

[a] Including eight strains with paradoxical effect. Despite a strain with caspofungin MIC of >16 μg/mL at first, repeat tests indicated that it was paradoxical effect, not true resistance (data not shown).

6. Antifungal drug resistance and treatment

Antifungal breakpoints for *C. auris* are not yet defined by the Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing. The US Centers for Disease Control and Prevention (CDC) set up, as it were, provisional breakpoints as follows: fluconazole (FLC) 32 μg/mL, amphotericin B (AMB) 2 μg/mL, micafungin (MCFG) 4 μg/mL, and caspofungin (CPFG) 2 μg/mL (Table 2) [14]. In a study authorized by the CDC, additional antifungal breakpoint is tentatively established such as 2 μg/mL for voriconazole (VRC), 8 μg/mL for echinocandins, and 128 μg/mL for flucytosine (5FC) (Table 2) [6].

In a current systematic review, the resistance rate is 44.3% for FLC, 12.7% for VRC, 1.3% for MCFG, 3.5% for CPFG, 15.5% for AMB, and 2.0% for 5FC [36]. Rarely, all three classes of resistance strains were found [6]. Resistance mechanism of *C. auris* only proved ERG11 mutations (F126T, Y132F, K143R) [6,36], but could not prove FKS 1 and FKS 2 gene mutations [36]. A limitation of this review article is that the resistance mechanism analysis is not determined [36]. Moreover, FKS1 mutation (S639F) was detected from pan-echinocandin resistant strains on a multicenter study [62].

Based on these previous reports, echinocandin may be recommended as an empiric therapy for *C. auris* infection. For multiple antifungal agent class resistance, some experts prefer combination therapy; however, it lacks decisive evidence [41]. As a future treatment option, phase 2 or 3 trial on ibrexafungerp (SCYNEXIS, Inc., formerly named SCY-078) is ongoing [42]. Ibrexafungerp is a 1,3-β-D-glucan synthase inhibitor [43] and has good activity *in vitro* toward *C. auris* with echinocandin resistance [44]. Another future treatment option is rezafungin (Cidara Therapeutics, Inc., formerly named CD101) [45]. Rezafungin is a newly developed echinocandin antifungal, and phase 3 clinical trial of this drug is initiated. CD101 keep low MIC for some *C. auris* strain with other echinocandin resistance [46].

7. Infection control

To prevent *C. auris* transmission through patients, devices, and environment, its presence should be quickly recognized and infection control intervention initiated. Strict infection control should be implemented by single-patient room isolation, strengthening the observance of hand hygiene, contact precaution, eradication from environment and patients, and surveillance for new cases.

If all patients with *C. auris* cannot transfer to a single-patient room, cohort isolation should be implemented using multiple patients' room. In this case, they should not be shared with patients with other multidrug-resistant organisms [4,47]. Contact precaution includes healthcare providers in contact with the patients and environments possibly contaminated by *C. auris* to wear gowns and gloves. Contact precaution duration is at least >3 months. Algorithm of negative culture confirmation to finish contact precaution is shown in Fig. 3 [47]. Axilla, groin, and previous detection sites should be considered as possible culture site [47]. Before performing the culture, we should wait at least 48 h after the administration of topical antiseptics and 1 week after systemic antifungals [47]. Culture interval may be hereafter reconsidered.

Hand hygiene using alcohol-based hand sanitizer or soap and running water should be performed before and after wearing the gown and gloves before contacting non-contaminated environment or other patients.

Generally, preventing transmission and eradication of *C. auris* are extremely difficult such as in other *Candida* species (needless infection control for no multidrug-resistant organisms). *Candida* species including *C. auris* remain alive on both wet (no nutrient agar) and dry (steel disks) environment for 7 days [48]. In another

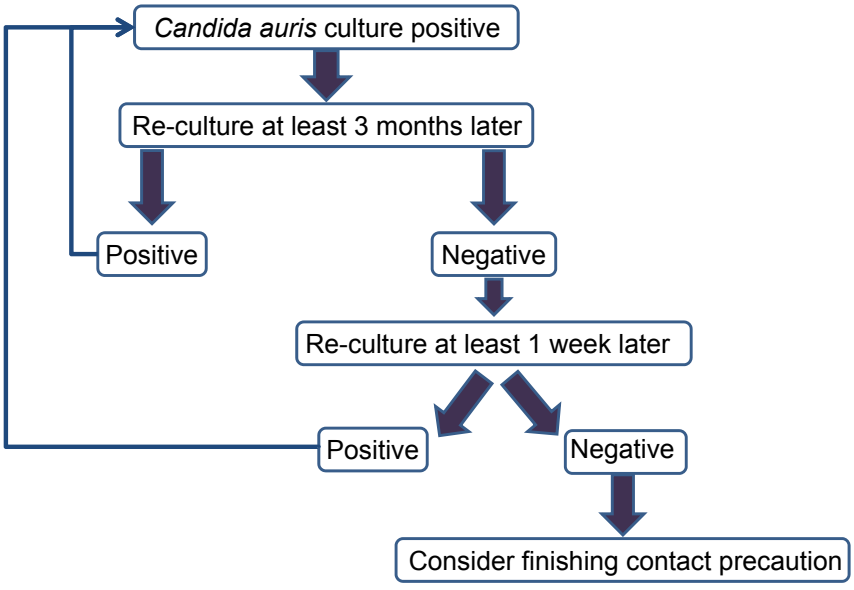

Fig. 3. Algorithm of negative culture confirmation to finish the contact precaution.

Table 3
The characteristics of 13 Japanese strains including minimal inhibitory concentration (μg/mL).

No.	TWCC No.	Specimen	Date isolated	Patient no.	FLC	ITC	VRC	5FC	MCFG	CPFG	AMB
1	13,878	Otorrhea	1997	Case 1	16	0.125	0.125	0.5	0.06	0.5[a]	0.25
2	13,846	Otorrhea (right)	2005	Case 2	4	0.03	≤0.015	≤0.125	0.03	0.25[a]	0.25
3	13,847	Otorrhea (left)	2005	Case 2	1	≤0.015	≤0.015	≤0.125	0.03	0.25[a]	0.25
4	50,952	Otorrhea	2008	Case 3	2	0.03	0.03	≤0.125	0.03	0.25[a]	≤0.03
5	58,362	Otorrhea	2008	Case 4	>64	0.25	2	0.5	0.125	0.125[a]	0.25
6	51,348	Otorrhea	2009	Case 5	4	0.06	0.03	2	0.03	0.25	0.5
7	51,372	Otorrhea	2009	Case 6	2	0.03	0.03	≤0.125	0.03	0.25	0.25
8	58,191	Otorrhea	2017	Case 7	4	0.06	0.03	0.25	0.06	0.5	0.25
9	58,321	Eustachian tube	2017	Case 7	4	0.06	0.03	0.25	0.125	0.5[a]	0.25
10	58,808	Otorrhea	2018	Case 7	2	0.03	≤0.015	≤0.125	0.06	0.25[a]	0.25
11	59,265	Otorrhea	2018	Case 8	1	0.03	≤0.015	0.25	0.03	0.25[a]	0.25
12	59,402	Otorrhea	2017	Case 9	2	0.06	0.03	0.5	0.03	0.25	0.25
13	59,659	Otorrhea	2019	Case 10	64	0.06	0.06	1	0.06	0.5	0.125

FLC: fluconazole, ITC: itraconazole, VRC: voriconazole, 5FC: flucytosine, MCFG: micafungin, CPFG: caspofungin, AMB: amphotericin B.
[a] With paradoxical effect.

study, *C. auris* and *C. parapsilosis* persist on plastic surface for at least 14 and 28 days, respectively [49].

To eradicate *C. auris* from the environment (including patients' room and mobile devices such as glucometers, temperature probes, blood pressure manchette, ultrasound probe, and carts), CDC recommends disinfectants for *Clostridioides difficile* spores [47]. Quaternary ammonium compound disinfectants are not recommended [4,47,50]. In *in vitro* studies, chlorhexidine gluconate (4% and 2% with 70% isopropyl alcohol), iodinated povidone (10%), chlorine-based disinfectant (1000 ppm), and hydrogen peroxide vapor (8 g peroxide/m^3) are effective [51,52]. In another *in vitro* study, *C. auris* on stainless steel and polyester surface regrew after contacting with sodium hypochlorite and peracetic acid; this result means it cannot be easily eradicated from the medical environment [53]. In two outbreak cases, patients' body wash containing chlorhexidine gluconate and environmental cleaning with hydrogen peroxide controlled this situation [54,55].

The requirement for screening and surveillance of *C. auris* is obscure. CDC suggests that screening be performed for healthcare providers in close contact with patients with *C. auris* and patients staying in healthcare facilities in countries with reported *C. auris* cases. Screening site should be bilateral axilla and groin [56]. Although the nose, mouth, external ear canals, urine, wounds, and rectum are usually less sensitive [56], these sites should also be screened in consideration of the patients' condition and disease. Surveillance requirement of *C. auris* is suggested for patients in the same facility or unit in case *C. auris* is detected [57]. In addition, the throat, vascular line, drain exit sites, drain fluids, and respiratory specimens are also suggested as surveillance sites [4]. CDC recommends surveillance duration of at least 1 month from no *C. auris*

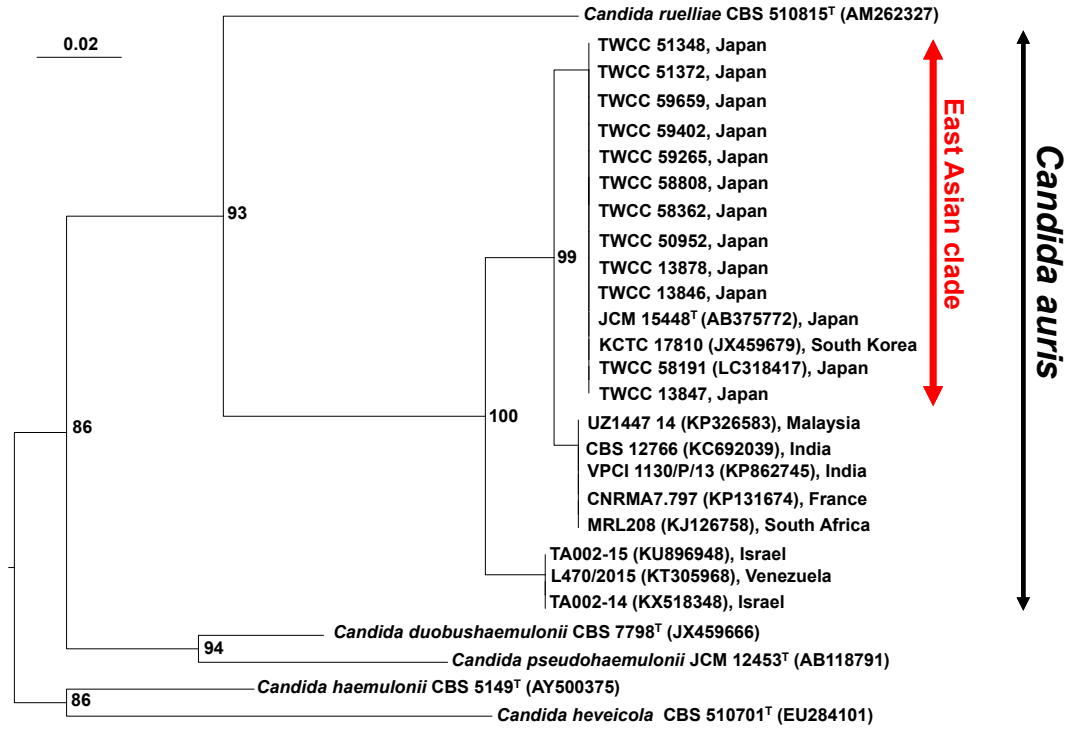

Fig. 4. Phylogenic tree using ITS sequences of *Candida auris* and related species (aligned by ClustalW and drawn by Tamura-Nei genetic distance model and Neighbor-Joining bootstrap analysis).

detection [57]. The algorithm used to determine contact precaution duration and confirmation of negative culture is shown Fig. 3 [47].

8. Characteristics of Japanese strains

In addition to those already reported [2,3], we identified seven strains of *C. auris* presented since 1997 at least in Japan, and all strains were detected from otorrhea or eustachian tube. Misidentification patterns were almost the same as in the previous reports; however, our strains were misidentified as *Candida sake* and *Saccharomyces kluyveri* on API ID32C (bioMerieux Japan Ltd.). These 13 strains have good susceptibility, except for two strains that are resistant to FLC and/or VRC, despite the high-frequency resistance of world strains (Table 3).

The phylogenic analysis using internal transcribed spacer (ITS) sequences was performed. Because our strains were independently classified as East Asian clade, they were identified as all native Japanese (East Asian) strains (Fig. 4.).

9. Future direction

Simple, quick, accurate and inexpensive diagnostic methods remain to be developed for more secure *C. auris* detection. For excellent diagnostic method, more exact epidemiology and distribution in general and medical environment will become clear. Unexpectedly, *C. auris* may extensively exist.

Regarding the notably antifungals resistance, *C. auris* have higher prevalence than other *Candida* species and other continental strains have higher prevalence than Japanese strains. A solution of resistance acquisition mechanism is also aimed, and Japanese strains may have special roles on this point. These problems may be solved by performing a whole genome analysis in the future.

C. auris colonization and infection are difficult problems for patients and medical worker. As regards the antifungals, development of disinfectants for *C. auris* eradication from patients and medical environment is expected.

10. Conclusion

C. auris is known as a new multidrug-resistant and emergent fungal pathogen. Therefore, the presence of this nasty pathogen should be recognized for its early detection and identification. Once *C. auris* is detected, many counterplans on infection control and treatment should be implemented.

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