An Observational Study of *Candida auris* Infections with Special Reference to the Clinicomicrobiological Problems Faced in Day-to-Day Practice at a Tertiary Care Hospital in Eastern India

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Background and study aim: *Candida auris* has emerged as a multidrug resistant fungus commonly associated with healthcare associated infections with immense importance in global healthcare setting. We attempted to carry out a census of various problems faced by clinical microbiologists and clinicians in establishing the fungus as a pathogen often prone to misidentification vis-à-vis its treatment and control in patients admitted to hospitals, especially in intensive care units.

Patients and Methods: This was a hospital based observational study with cross-sectional design. During the study period which encompassed the COVID-19 pandemic, critically ill patients in intensive care units with corroborating history, clinical presentation with high degree of suspicion towards a *Candida auris* candidemia responding poorly to antibacterial treatment were identified. Blood culture from the patients were collected and processed as per standard guidelines. Both conventional and automated identification systems were used to identify *Candida auris* followed by antifungal susceptibility testing by disc diffusion methods and broth microdilution.

Results: Sixty patients were identified as being potentially infected with *C. auris*; six of which demonstrated growth of the fungus on blood culture, detected both by conventional and automated methods. All the patients had invasive disease, fever being the constant clinical presentation; four had history of road traffic accident and received primary care elsewhere; all six patients were on broad spectrum parenteral antibacterial antibiotics for considerable duration with no clinical improvement.

Conclusion: A positive clinical correlation and high mycological suspicion is essential in diagnosis of *Candida auris* infections. Multidisciplinary involvement, administrative will, strict adherence to infection control strategies plays a leading role in controlling *Candida auris* infections.

INTRODUCTION

Candida auris is a non-albicans *Candida*; a multi-drug resistant yeast-like fungus and a relatively novel member belonging to the *Candida haemulonii* complex (Metchnikowi-aceae clade) which have been reported to cause both systemic and localized infections with high morbidity and mortality and considered as one of the most serious emerging pathogens, with grave public health implications **[1]**. It was first described in 2009, after being isolated from the external ear canal of an inpatient in a Japanese hospital **[1,2]**. Since then, reports of *Candida auris* infections, including fungemia, wound infections, otitis etc. have been reported globally, gaining notoriety over years. Apart from being a multidrug resistant fungus due to its biofilm forming ability with eventual reduction in activity of antifungal drugs, the fungus has also been shown to form non-dispersible cell aggregates, which supports its persistence for longer time in environment in addition to its thermotolerant and salt tolerant properties **[3-5]**. The initial 3 cases of hospital acquired infection due to *C. auris* reported in 2011 from South Korea highlighted the fact that *Candida auris* can be commonly misidentified as *C. haemulonii, C.*

famata, C. sake, Saccharomyces cerevisiae, Rhodotorula glutinis, C. lusitaniae, C.guilliermondii or *C. parapsilosis* by the automated identification systems like VITEK2 (bioMérieux, Marcy I'Etoile, France) and other phenotype-based identification systems **[2,4]**. Definite confirmation of the species is possible either by Matrix-Assisted Laser Desorption/ Ionization-Time Of Flight-Mass spectrometry (MALDI-TOF-MS) with upgraded database or by sequence analysis of the D1/D2 domain of the large ribosomal subunit (LSU) of 26S rRNA gene and the internal transcribed spacer (ITS) regions of the nuclear rRNA gene operon, which are not frequently available in most diagnostic laboratories **[6-8]**.Unlike other Candida species, the fungus has the propensity to acquire rapid resistance to azoles, polyene and even echinocandins. This 'difficult to identify', 'difficult to treat' fungus continues to remain a proverbial headache for clinical microbiologists and clinicians, globally.

PATIENTS AND METHODS

Study design: This was a hospital based observational study with cross-sectional design.

Study settings: The study was carried out from January, 2020 to June, 2021at the department of Microbiology at an apex hospital, at a time which paralleled the COVID-19 pandemic.

Study patients: We actively searched for critically ill patients in intensive care units of our hospital and found patients with worsening symptoms, not responding to broad spectrum antibacterial antibiotics. The febrile patients attending outdoor facility or patients with blood stream infection with confirmed bacterial aetiology and those responding to antibacterial antibiotics were excluded from the study population.

Sample size: Taking the prevalence of *Candida auris* candidemia in intensive care setting as 5.3% **[7]**, our target sample was calculated as sixty patients.

Study procedure: Serial blood culture of these patients was carried out both by conventional and automated procedures. Two sets of aerobic and anaerobic blood culture (with collection of 10-20ml of blood from each patient per 50 ml bottle of Brain Heart infusion broth, prepared inhouse) at a gap of one week were taken, incubated at 35-37°C. We waited for no less than 48 hours for growth signal or appearance of growth followed by identification as per standard guidelines **[7,10]**. The positive blood culture bottles were sub cultured on 5% Sheep Blood agar plate (SBA), MacConkey Agar (MAC), Sabouraud Dextrose Agar with and without Chloramphenicol (SDA/SDCA) and a selective CHROMagar Candida medium (Difco, Becton Dickinson, Baltimore, MD, USA), as depicted in **Figures 1 to 4 [9]**. We observed for growth on all the inoculated media after incubation at 35°-37°C maintaining aerobic conditions for a minimum of 48 hours. Gram stain from the growth on culture plates and SDA slope were carried out with the common finding of a Gram positive yeast-like fungus. Germ tube test was done using *Candida albicans* ATCC 90028 as control, however no germ tube formation was noted in the test isolates. On CHROMagar Candida medium (Difco, Becton Dickinson, Baltimore, MD, USA) we recovered moist, convex, colourless colonies in the initial 24 hours which gradually turned pink purplish on further incubation **[7,9,10]**. We tested the ability of the yeast of producing pseudo hyphae or other structures by streaking the isolates on cornmeal agar (CMA) plates and incubating the inoculated streak under a sterile coverslip at 30°C for 48 h (Dalmau culture) **[9-12]**. The capacity to form aggregates was evaluated microscopically by dissolving one *C.auris* colony in 20mcL of normal saline. The findings from Dalmau culture were non-contributory for all six isolates **[7-10]**. Following the conventional techniques, we ran the same isolates on automated identification system (VITEK2, bioMérieux, Marcy I'Etoile, France) which corroborated with our findings on conventional system. Antifungal susceptibility test (AFST) was done by disc diffusion method per CLSI guidelines **[10,12]** using Itraconazole, Voriconazole, Anidulafungin, Caspofungin discs etc. and E-test as per standard guidelines. The disc diffusion results of AFST were confirmed by performing broth microdilution (BMD), which continues to remain the gold standard in carrying out antifungal susceptibility **(Figures 5 and 6)**. We collected the data, enlisted on Microsoft Excel, and analyzed the same as our study continued.

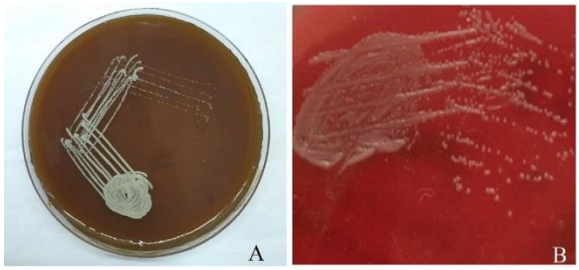

Figure 1
Legend: Growth of *Candida auris* on Sheep Blood agar (SBA) plates (A and B)
Caption: Blood agar plate showing growth of small,moist, convex, transluscent colonies having a diameter of 3-4 mm with no distinct odor**(A)**; on close inspection moist, convex, transluscent colonies are noted with hemolysis **(B)**

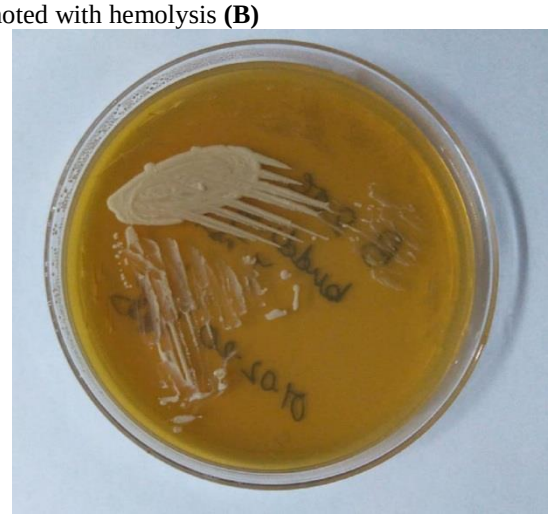

Figure 2:
Legend: Growth of Candida auris on Sabouraud dextrose agar (SDA) plates
Caption: Sabouraud dextrose agar plate showing growth of small,moist, convex, white to cream-colored colonies with a certain yeasty odor.

Figure 3:
Legend: Growth of Candida auris on CHROMagar Candida medium
Caption:CHROMagar Candida medium showing growth of showing moist, convex, transluscent, pink colonies.

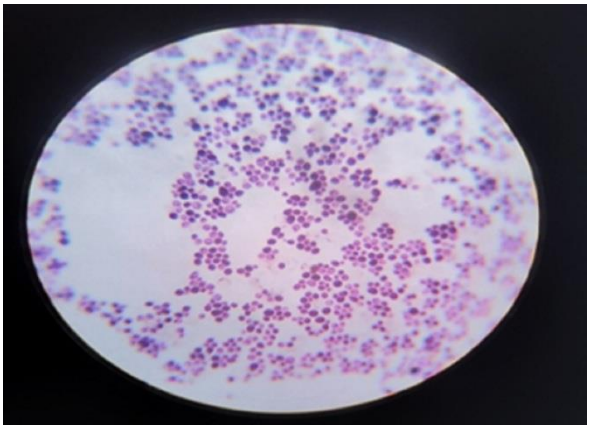

Figure 4:
Legend:: Gram stain findings
Caption: Gram stained smear from the isolated colony onCHROMagar Candida medium showing Gram positive yeast-like structures with budding.

Figure 5:
Legend:: Antifungal susceptibility testing by Disc diffusion method
Caption: Antifungal susceptibility test done by disc diffusion method on Mueller Hinton agar using Itraconazole, Voriconazole, Nystatin etc.discs.

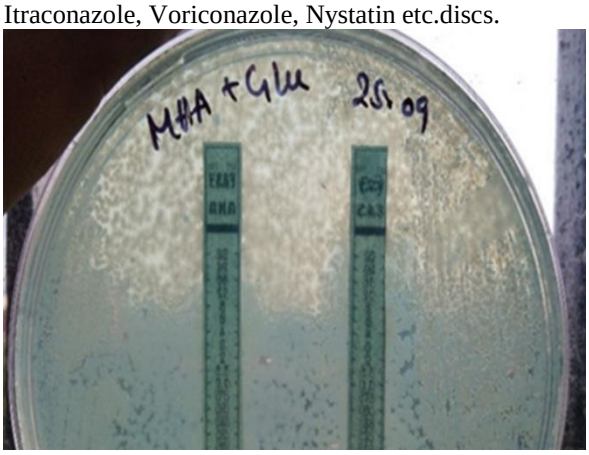

Figure 6:
Legend: Epsilometer test (E-test) on Mueller-Hinton agarwith glucose.
Caption: Epsilometer test done on Mueller-Hinton agar with glucose using Anidulafungin, Caspofungin strips; revealed resistance to both.

VITEK2 (bioMérieux, Marcy I'Etoile, France) system identified each of the six isolates as *Candida auris* with 99% probability. As VITEK-2 database was not supportive of *Candida auris* antifungal sensitivity, further testing was done by disc diffusion method and E-test, in accordance with international guideline and checked by broth microdilution (BMD) **[10,11]**. The CLSI recommends Mueller-Hinton agar with 2% glucose and 0.5 µg/ml methylene blue dye (GMB) for disc diffusion technique as it enhances reproducibility. The addition of glucose supports fungal growth whereas, methylene blue accentuates the zone edge definition. CLSI dictates similar procedure for inoculum preparation in both disc diffusion and broth dilution based methods with a final stock suspension of 1×10^6 to 5×10^6 cells per ml. A sterile cotton swab was dipped into the isolate suspension, rinsed firmly against the inside wall of the tube to remove excess fluid, and then used to streak the entire agar surface a total of 3 times, with rotation of the plate approximately 60° each time, ensuring even distribution of the inoculum over the agar surface. The agar plates were dried for a minimum of 3 minutes and a maximum of 15 minutes, the antifungal discs were applied maintaining aseptic techniques, maintaining at least 24mm distance between two disk centres. The plates were incubated at 35°C±2°C for no less than 24 hours, the zone diameter for each disk is measured to the nearest millimetre at the point in which there is a prominent reduction of growth. CLSI document M60 provides zone diameter interpretive criteria for Caspofungin, Fluconazole, and Voriconazole. At 100% growth inhibition, the zone diameter endpoints were measured with measuring scales and compared with standard zone diameters, as per CLSI M44, 3rd Edition **[10-11]**.

Statistical analysis

The collected data were collected and analyzed using Microsoft Excel as the study continued.

RESULTS

We reached at a diagnosis of *Candida auris* as the etiological agent of febrile illness in six out of sixty cases under investigation. The yeast was isolated repeatedly and conclusively by both automated and conventional blood culture systems which correlated with poor and deteriorating clinical condition of the patients. The mean hospital stay of the patients in our study was 14 days. All the patients received initial treatment outside our institution and were admitted to our intensive care units. We identified sixty suspected cases of *C. auris* candidemia, out of which we carried out thorough investigations on six patients with successful isolation, identification, and susceptibility pattern of the fungus (**study work flow demonstrated in Figure 7**)

Fever was the common symptom. Two of our patients had history of road traffic accident. All of them were on mechanical ventilator support and received initial care outside our institution. 1 of the 6 patient was on Total parenteral nutrition (TPN) and 1 required renal replacement therapy (RRT). Laboratory parameters of the patients showed a normal leucocyte count, with mild neutrophilia, raised CRP and Procalcitonin, normal serum electrolytes, mild transaminitis, raised serum globulin, which remained unchanged during the whole course of their stay. We could not reveal any bacteriological, parasitological or viral etiology of fever, even after intensive work up **(Table 3.1)**

The antifungal susceptibility testing (AFST) of the isolates revealed; all resistant to Nystatin, Fluconazole, Voriconazole; 4 out of 6 isolates were found to be sensitive to Anidulafungin **(Table 3.2)**.All six patients were on intravenous broad spectrum antibacterial antibiotics before we could reach at a diagnosis of *Candida auris* candidemia following which they were started on intravenous echinocandin monotherapy like Anidulafungin 200 mg loading dose as slow infusion with normal saline and then 100 mg once per day for 14 days or in combination with ketoconazole **[12-14]**. After initial two days of antifungal administration the patients showed marked clinical improvement. Fever started subsiding and subsequent blood cultures taken after 7 days and 14 days, **[15]** were sterile and patient was clinically stable. There was no marked change in their laboratory parameters during the whole course of stay. Environmental and samples from other patients in near vicinity were requested from the treating units, as detection of this fungus as a coloniser has great significance in assessment of clinical burden of infection **[16-20]**.

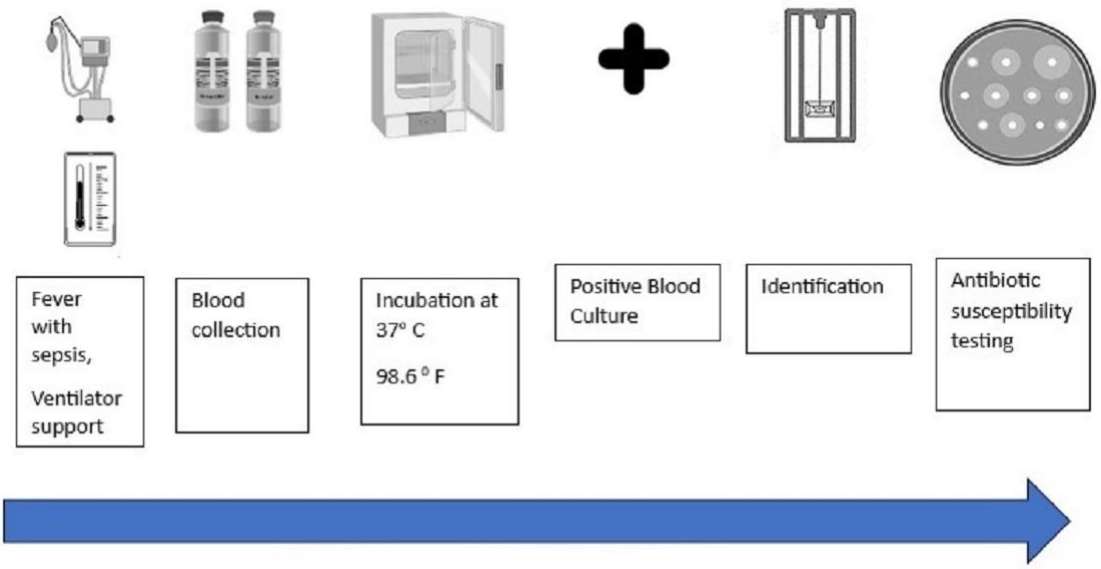

Figure 7:
Legend: Our study workflow
Caption: Our study workflow involved selection of patients with suspicion of *Candida auris* infection, followed by collection of blood for blood culture, isolation, identification of the fungus and carrying out the antifungal susceptibility testing.

Table 3.1: Details of the patients with culture confirmed *Candida auris* candidemia

Ward	Age(in years)	Sex	Residence (Rural, Urban)	Symptomatology	Hospital stay (in days)	Total Leucocyte count (per mm^3) at admission	Total Leucocyte count (per mm^3)at discharge	CRP/ mg/dl) Procalcitonin (ng/ml) at admission	CRP/ mg/dl) Procalcitonin (ng/ml at discharge	Serum Alanine aminotransferase (ALT) / Aspartate aminitransferease (AST) in U/litre
TCC-ICU 1	19	F	Rural	Fever, post-traumatic seizure, altered sensorium.	15	10,000	9000	1.2/0.5	1.2/0.5	60/70
CCU 1	15	M	Urban	Fever, anuria, headache.	14	9600	10000	1.4/0.5	1.2/0.5	70/80
TCC-ICU 2	56	M	Rural	Fever, subdural hemorrhage, long bone fractures	14	7800	9000	2.4/1	2.4/0.5	50/60
TCC-ICU 3	32	M	Urban	Fever, subarachnoid hemorrhage, altered sensorium	13	10900	9000	01-Feb	1.2/0.5	80/70
CCU 2	52	M	Urban	Fever, respiratory distress.	16	9900	8000	1.8/1	1.2/1	60/50
TCC-ICU 4	32	F	Urban	Post-traumatic fever, wound infection, aural discharge.	12	6000	6000	2	1.2	70/60

Table 3.2: Table showing antibiogram pattern of *Candida auris* isolates from blood culture, antifungal susceptibility testing done by disc diffusion methods and broth microdilution.

Antifungal drugs	Tentative minimum inhibitory concentration breakpoints of Candida auris by Centers for Disease Control and Prevention (in micrograms/ml)	TCC-ICU 1	CCU 1	TCC-ICU 2	TCC-ICU 3	CCU 2	TICU 4
Fluconazole	≥32	R	R	R	R	R	R
Voriconazole	NA#	R	R	R	R	R	R
Ketoconazole	NA#	R	R	R	R	R	S
Itraconazole	NA#	R	R	R	R	R	R
Nystatin	NA#	R	R	R	R	R	R
Amphotericin B	≥2	R	R	R	R	R	R
Micafungin	≥4	R	S	R	R	S	R
Anidulafungin	≥4	S	S	S	R	R	S
Caspofungin	≥2	R	R	R	S	R	R

(R= Resistant, S=Sensitive, NA= not applicable, # =antifungal susceptibility testing done by disc diffusion method for the following antifungals: Voriconazole,Ketoconazole,Itraconazole,Nystatin)

DISCUSSION

Through this study of ours we tried to conduct a microbiological review of suspected *Candida auris* infections and actively searched for confirmed cases at our hospital over a considerable amount of time and hammer on the difficulties faced in day to day practice. We progressed with the premeditated knowledge of this yeast being a nosocomial colonizer often isolated from surfaces, most often multi-drug resistant, difficult to treat, patients required strict isolation facilities and a dedicated team-based treatment often involving multiple disciplines and merits for tracing the contacts and environmental sampling **[21-24]**. While selecting our patients we followed studies conducted by **Rudramurthy et al** and **Chowdhary et al**. which revealed that *C. auris* accounted for >5% Candidemia in Indian intensive care units and almost 30% of infections in individual hospitals [25,28] *C. auris* Candidemia cases have been reported across 5 continents. The risk factors for developing *C. auris* infections were almost similar in most centers, which included; abdominal surgeries, prolonged hospital stay, ICU admission, diabetic state, presence of indwelling central venous catheter etc. [24-26]. Significance of *C. auris* isolation depended only on clinical correlation. Our study progressed in parallels with the COVID-19 pandemic. All sixty suspected cases were from various intensive care units and were having risk factors for developing *C. auris* infections, however we could thoroughly investigate six confirmed cases as we faced logistical and practical difficulties in recruiting and investigating all suspected cases. The kin or next of kin of most suspected patients were unwilling to undergo further investigations.

This fungus is known to pose difficulty in identification as a 'pathogen' with automated systems and require clinical correlation and close surveillance of the patients and environment before reaching at a diagnosis. During our study we carried out serial blood culture of patients with the targets of ruling out bacterial etiology and isolation of yeast, either by conventional and/or automated blood culture system and followed by identification by conventional methods including CHROMagar Candida medium and VITEK-2 followed by antifungal susceptibility tests (AFST) by disc diffusion method and E-test, using Itraconazole, Voriconazole, Anidulafungin, Caspofungin discs etc followed by confirmation with broth microdilution (BMD). Misidentification of *Candida auris* has been a known hindrance in initiation of prompt and specific therapy, since discovery. In an exhaustive Indian study by **Kathuria et al** [**4**], the investigators used Internal transcriber spacer(ITS)sequencing for

confirmation of 88.2% of 102 yeast isolates as *Candida auris* which were previously misidentified as *C. haemulonii* or *C. famata* with the VITEK system. Several other studies impress upon the fact that *C. auris* continues to remain elusive in most laboratories as most commercially available identification systems do not have an updated yeast database. The high-end laboratories can utilise Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF-MS) which is considered a rapid and a dedicated system for diagnosis of *Candida auris*, however availability is still restricted in centres like ours. We found instances when researchers have tried to find the reason behind this tendency of *Candida auris* to be misidentified as something else. **Chatterjee et al.** and **Sharma et al [17,18]** in their studies involving Whole Genome Sequencing (WGS) have showed close phylogenetic resemblance of *Candida auris* and *Candida lusitaniae*, both being intrinsically resistant to most antifungals. *C. auris* has been demonstrated to have pathogenicity resembling *C.albicans* by **Borman et al**. In other studies, both *C.auris* and *C.albicans* demonstrated biofilm forming ability, adherence to polymers, making the pathogen more persistent, more drug resistant in a healthcare setting **[23,24,26]**.

Lockhart et al in their collaborative study under the aegis of Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, with isolates from 54 patients with *C. auris* infection from Pakistan, India, South Africa, and Venezuela which showed that 93% resistance to Fluconazole, 35% to Amphotericin B, 7% to Echinocandins; near about 41% were resistant to 2 antifungal classes, and 4% were resistant to 3 classes **[27,28]**. **Rudramurthy et al** and some other investigators have shown Posaconazole and Isavuconazole of having promising in-vitro activity against *C.auris*. However, over the years Echinocandins became the first-line therapy, with limited activity against *C.auris* biofilm **[24,25]**. Pioneering studies by **Kim et al.** and **Lee et al** on multi-drug resistance of *C.auris* on 15 and 3 isolates, respectively from South Korea, were instrumental in making the scientific community aware of an emerging drug resistant fungus **[2,3]**. Both studies revealed resistance of the agent to conventionally used antifungals like Amphotericin B (AMB) and all azoles. In path breaking research conducted by **Chowdhary et al** in 2013 and 2014, 3 hospitals in New Delhi were identified to be housing *C.auris* infection demonstrating significant resistance to Fluconazole (FLU) and 5-flucytosine (FC) and showed elevated minimum inhibitory concentrations (MICs) of voriconazole (VRC) and Caspofungin (CFG)**[19-20]**.

Our understanding of *Candida auris* is evolving. As we continue to learn about the fungus, few possibilities become more probable: high likelihood of the MDR pathogen spreading to unaffected parts of our planet which would eventually tax our laboratories, pharmaceuticals and healthcare delivery systems with greater economic burden, as we would require multifaceted diagnostic tools and more expensive antifungal treatment. Global preparedness to face a future fungal pandemic is a telling requirement.Management, control and prevention of *Candida auris* leaves ample space for improvement in strategies for containment of outbreaks, multidisciplinary approach and early initiation of treatment, improvement in hospital infection control, including disinfection, hand washing, strict adherence to bio-medical waste disposal guidelines, patient isolation, barrier nursing, restriction of footfalls in hospital environment. High index of suspicion is the key to a fruitful diagnosis of *Candida auris*. Prevention can be done by contact investigation to identify and detect transmission by collecting swab sample from body sites mainly the skin folds like axilla, groin as well as from patient's environment. All *Candida auris* patient should be managed by placing in a single room with contact precaution. When more than one patient with *C. auris* are identified, infection control measures should be performed. Centers for Disease Control and Prevention (CDC) has laid down guidelines which prescribe daily disinfection of room surfaces with high level disinfectant (HLD), medical equipments by autoclaving or ethylene oxide or gas plasma sterilization. Regular dedicated oral decolonization with 0.2% chlorhexidine mouthwash, 1% chlorhexidine dental gel in ventilated patient have shown to reduce colonization. Chlorhexidine impregnated protective disk for central vascular catheter exit sites may be used to reduce central line associated blood stream infection. For terminal cleaning, fogging by hydrogen peroxide vapors been used to disinfect patients' room. Several newer antifungals are in various stages of development against this fungus and are showing

promising results e.g. Ibrexafungerp (IBX; SCY-078, SCY078 and MK-3118), Rezafungin (RZF; CD101 and SP3025), Manogepix (MGX; APX001A and E1210), Fosmanogepix (FGX; APX001 and E1211), Olorofim (F901318), Opelconazole (OPC; PC945), Quilseconazole (VT-1129), Oteseconazole (VT-1161), VT-1598, ATI-2307, MGCD290 and VL-2397 **[29-31]**. For all practical purposes, we can carry out a multicentric study analysing past microbiological records for a minimum one-year duration of patients with high-risk attributes along with enhanced surveillance of laboratory settings for identification of *C.auris* , which can play vital role in preparing strategies for future prevention of infections.

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Conflict of interest: None

Ethical consideration;

Permission and official approval to carry out the study was obtained from the Institutional Ethics Committee (IEC), IPGMER and SSKM Hospital, Kolkata, West Bengal, India before carrying out our study. All patients' kin signed a written informed consent before inclusion into this study.

HIGHLIGHTS

1. Identification, management and prevention of *Candida auris* infections continue to pose significant problems in global healthcare settings.
2. Awareness amongst healthcare workers and patients is the only way out of this problem.
3. A high index of suspicion of the clinical microbiologist and treating physician are essential ; treatment options continue to be limited.

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