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CANDIDA AURIS- AN EMERGING THREAT IN ICU

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ABSTRACT

Candida auris is an emerging multidrug resistant fungus that has caused outbreaks of invasive infections in healthcare facilities. Infections can occur in patients of all ages, but most infections have been reported in adults. Isolates were identified by Vitek 2 and also by conventional method. AST was done by both broth microdilution and disk diffusion methods. Of the 100 isolates, *Candida auris* was isolated in 12 cases. Fluconazole was resistant in 11(91.67%) isolates but all the isolates were found sensitive to Voriconazole (100%) by both the methods. Appropriate infection control measures should be instituted to contain this emerging threat.

KEYWORD: Candidemia; *Candida auris*; ICU.

INTRODUCTION

Candida auris is an emerging multidrug resistant fungus that has caused outbreaks of invasive infections in healthcare facilities around the world and it is considered a major threat to healthcare settings.[1-3] *Candida auris* was first reported in 2009 following isolation from the external ear canal of a patient in Japan.[4] Candidemia caused by *C. auris* was reported first in 2011.[5] India reported the first case of candidemia due to this yeast in 2013.[6] *Candida auris* has been reported from six continents and has caused outbreaks in places such as Colombia, India, South Africa, Spain, and the United States.[1-3] Recently, *C. auris* was found to be the second most prevalent species causing candidemia in a tertiary care trauma centre in Delhi, India, warranting more effective infection control practices to prevent its spread.[7] Healthcare facilities have reported *C. auris* outbreaks in critically ill hospitalized patients with high crude mortality rates (30-72%).[1-3] Risk factors of candidemia include recent major surgical procedures, diabetes, use of broad spectrum antibiotics, long-term hospitalization, and the presence of devices, including breathing tubes, feeding tubes, and central venous catheters. Risk factors for candidemia differ by the population affected.[3,8] Infections can occur in patients of all ages, but most infections have been reported in adults.[8] Resistance of *C. auris* to all the three main classes of antifungals namely azoles, polyenes, and echinocandins has been reported.[9] In vitro, more than 90% of *C.auris* isolates have shown resistance to fluconazole.[10] Indeed, echinocandins are the first-line therapy for *C.auris* infection. Invasive infections of *C. auris* are fatal unless early detection and treatment is initiated.[11] Acquired resistance while on treatment is a concern. Echinocandin resistance has developed in patients with *C. auris* infection while receiving echinocandin treatment.[12] *C. auris* persists in the environment for months, and persistent environmental contamination, contaminated medical equipment and other fomites are believed to play a role in nosocomial *C.auris* transmission.[13] Survival of *C. auris* in the hospital environments may be promoted by its capacity for salt tolerance and cell aggregation into large- and difficult- to- disperse aggregates. Moreover isolates exhibit thermotolerance up to 42°C and form biofilms on intravascular catheters, which is an added advantage for survival and pathogenesis.[6]

MATERIALS AND METHODS

This study was conducted after obtaining approval from institutional ethical committee. Written informed consent was not obtained because the data were analyzed retrospectively.

Study samples: Hundred consecutive candida isolates isolated from blood.

Isolates were identified by Vitek 2 (bioMérieuxInc., Durham, USA) version 8.01 using a YST ID card. Identified *Candida auris* strains were also further

identified by conventional methods. Gram- stained smear from the positive blood culture by BacT-ALERT showed Gram positive oval budding yeast-like cells without pseudohyphae. Sabouraud dextrose agar (SDA) (HI Media, Mumbai) showed cream-colored colonies, and CHROM agar Candida (HiCrome™ HiMedia, Mumbai) showed cream colonies with purple tinge after 48 h of incubation. Growth patterns at different temperatures, 37°C, 42°C, and 45°c, were also observed.[14] SDA plate incubated at 42°C also grew yeast-like pasty colonies. The isolates were negative in germ tube test and there was no hyphae/ pseudohyphae on the corn meal agar in dalmau method. No discrepancy was found in the identification between the two methods.

Antifungal susceptibility tests (AST) was done by both broth microdilution and disk diffusion methods. MIC of fluconazole and voriconazole against the isolates were determined by broth micro dilution method following the M27-A3 CLSI document.[15] There are no established MIC breakpoints at present for *C. auris* drug susceptibility interpretation. The CDC has applied conservative breakpoints developed for other Candida spp. to *C.auris* for epidemiological purposes. The breakpoint for fluconazole was arbitrarily set at ≥32µg/ml and for voriconazole ≥2µg/ml.[16] Disk diffusion testing was performed as described in CLSI document (M44-A2). Briefly, 90-mm-diameter plates containing Mueller-Hinton agar supplemented with 2% glucose and methylene blue (HiMedia, Mumbai) were used. A swab dipped in a cell suspension adjusted to 0.5 McFarland standard turbidity was used to inoculate the agar. The plates were subsequently incubated at 35°C and read at 24 h. The zone diameter endpoints were read at 100% growth inhibition with calipers. Fluconazole (25 µg) and Voriconazole (1µg) disks were purchased from Himedia Laboratories, Mumbai. Control strains *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used.[17] Each isolate was tested in duplicate by both disk diffusion and microbroth dilution methods and no discrepancy was found in the results by the two methods.

RESULTS

In the present study, out of the total 100 *Candida* spp. isolated from blood culture of patients, *Candida auris* was isolated in 12 cases. Other 88 isolates comprised of *C. albicans* (34%), followed by other Non-albicans *Candida* (NAC) spp. like *C. tropicalis* (20%), *C. parapsilosis* (12%), *C. krusei* (6%), *Kodamea ohmeri* (5%), *C. famata* (4%), *C. pelliculosa* (3%), *C. utilis* (2%), *C. dubliniensis* (1%), and *C. lipolytica* (1%).

All the 12 cases of *C. auris* were from ICU set up with age ranging from 15years to 65 years. AST was conducted for all the 12 isolates by both micro broth dilution (M27-A3) and disk diffusion method (M44-A2). MIC of Fluconazole was ≥64 µg/ml for 11 isolates and ≤8 µg/ml for one isolate. For Voriconazole, MIC was ≤1 µg/ml for all the 12 isolates. Fluconazole was found resistant in 11 (91.67%) cases but all the isolates were sensitive to Voriconazole (100%) by disk diffusion method.

DISCUSSION

The present study highlights that *Candida auris* has emerged as a significant pathogen in India.

All candida isolates from sterile sites should be identified at the species level to guide antifungal therapy and from the non-sterile sites for infection control and surveillance purposes as recommended by CDC.[18,19]

Early identification and reporting of *C. auris*, will improve better patient outcome and provide better insight to the magnitude of the infection impacting global intervention plans.[20]

A number of studies determined different possible risk factors for developing *C. auris* infection/colonization which includes the presence of tracheostomies, ventilators, prior antibiotic use, ICU stay and comorbidities such as DM, CKD and lung disease.[21-26] In our study, the majority of these patients had indwelling catheters 11(91.67%), were on a ventilator 6(50%), admitted to the ICU 12 (100%), and/or received multiple courses of antibiotics during their hospital stay 9 (75%), comorbidities like diabetes mellitus 5 (41.7%), chronic kidney disease 3(25%) and HIV 1(8.3%) were present in 9 (75%) cases (Table1). These factors are significant to consider when candida infection is suspected in order to guide management and infection control measures.

Table 1: Descriptive statistics of *C. auris* cases.

Categories	Overall (N=12)
AGE GROUP: > 60 years	2(16.67%)
MALE	7 (58.33%)
DURATION OF HOSPITAL STAY:<30 days	11(91.67%)
COMORBIDITIES	9(75%)
Diabetes mellitus	5
Chronic kidney disease	3
HIV	1
ICU ADMISSION	12(100%)
INDWELLING CATHETER	11(91.67%)
SURGERY	4(33.33%)
PRIOR TREATMENT WITH FLUCONAZOLE	4(33.33%)
PRIOR TREATMENT WITH BROAD SPECTRUM ANTIBIOTICS	9(75%)
CONCOMITANT INFECTIONS	11(91.67%)
MRSA	2
MSSA	4
KLEBSIELLA SP.	4
ENTEROCOCCUS FAECALIS	1
ANTIFUNGAL TREATMENT RECEIVED	
FLUCONAZOLE	4
VORICONAZOLE	1
AMPHOTERICIN B	5
CASPOFUNGIN	2
DIED	6(50%)

The reported mortality rates attributable to invasive *C. auris* infection range from 30%-59% globally.[16,24] Crude in hospital mortality rates for *C. auris* candidemia are estimated to range from 30%-72%.[27] The overall infection fatality rate in our study was 50%.

The fact that 6 patients died while on antifungal treatment raises the possibility of treatment failure despite the antifungal results in vitro. It is still unclear how well in vitro AST results correlate with the in vivo performance of antifungal agents against *C.auris* infection. However, we must take into account other possible causes of death, such as underlying comorbidities and uncontrolled source of infection.

CONCLUSIONS

The management of infections caused by these superbugs should be guided by antifungal susceptibility results. Appropriate infection control measures, including isolation and strict hand hygiene practice, should be instituted to prevent transmission and contain this emerging threat. High level of knowledge and alertness by physicians and health care settings, would help to control the spread and improve diagnostic and therapeutic strategies.

LIMITATION OF THE STUDY

- Antifungal tests were done with only fluconazole and voriconazole. Although echinocandins are the drug of choice, antifungal test was not done with it because of unavailability.
- Molecular methods could not be done for species confirmation of the isolates.

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