



Original Article

Candida auris: An Emerging Multidrug-Resistant Pathogen Alarming Highest Level of Concern, Case Series

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ABSTRACT

Candida auris is an emerging multidrug-resistant fungus that causes life-threatening healthcare-associated infections. This fungal pathogen has been designated as an urgent threat by the US Centers for Disease Control and Prevention and classified in the Critical Priority group by the World Health Organization. In this report, we describe three cases of nosocomial fungemia caused by *C. auris*. All three patients exhibited persistent fungemia for approximately 10 to 31 days after their admission to our hospital. We collected patient history and samples for our study. Blood samples were sent to the microbiology laboratory for processing. The isolates obtained were identified as *C. auris* through MALDI-TOF MS. Antifungal sensitivity testing was conducted using the VITEK-2 compact. All three isolates were found to be pan-resistant to these antifungal agents. Tragically, all three cases resulted in fatal outcomes. The pan-resistance to available therapeutic options is concerning in the hospital and necessitates prompt management.

Keywords: *Candida auris*, resistance, antifungal agents, MALDI-TOF.

INTRODUCTION

Multidrug-resistant *Candida* species that are emerging include *C. glabrata*, *C. krusei*, *C. lusitaniae*, members of the *C. guilliermondii* complex, *C. kefyr*, members of the *C. haemulonii* complex, and *C. auris* (Colombo et al., 2014). The World Health Organization (WHO) classified *C. auris*, a multidrug-resistant fungal pathogen, as a critical priority pathogen (J, 2018). The World Health Organization (WHO) intends this formal recognition to guide research, development, and public health action in the context of invasive fungal diseases (J, 2018). It is a member of the ascomycetous (Hemiascomycetes) *Clavispora* clade in the *Metschnikowiaceae* family, within the order *Saccharomycetales*. The term 'auris' is derived from the Latin word, which means 'ear.' It was first discovered in the ear canal of a 70-year-old Japanese patient in 2009 during his hospitalization (Satoh et al., 2009) (Lee et al., 2011). The risk of an epidemic is high because *C. auris* can persist in the environment and is resistant to common disinfectants (Schelenz et al., 2016). The high rate of transmission of *C. auris* is due to its ability to colonize the skin and other body sites. The formation of biofilm helps it to persist for weeks on abiotic surfaces and equipment (Ledwoch & Maillard, 2018). Clinical alerts are being issued by the Centers for Disease Control and Prevention (CDC) occasionally to alert people to the development of systemic candidiasis (Fan et al., 2021). Healthcare-acquired transmission of *C. auris* typically affects individuals with chronic illnesses, individuals with invasive medical devices such as mechanical ventilation, tracheostomies, feeding tubes, and urinary catheters, and prolonged hospital stays (Ahmad et al., 2020) (Lesan et al., 2019). Echinocandin is the first-line treatment for the most invasive *Candida* infections, as it is generally resistant to other antifungals. Echinocandin resistance, along with resistance to azoles and amphotericin B (pan-resistance) isolates, is a significant clinical and public health concern (Spivak & Hanson, 2018). In light of the growing era of multidrug-resistant *C. auris* strains, it is imperative to develop novel therapeutic strategies. The development of new antifungal agents and the combination of existing drugs are currently being streamlined for the prevention of this multidrug-resistant isolate infection.

METHOD

A rapid and accurate diagnosis of *Candida auris* is essential. We collected the medical histories of three patients whose blood samples tested positive for *C. auris* at our hospital. The growth of *C. auris* on 5% Sheep Blood agar appeared as small, white, opaque, non-hemolytic colonies, while MacConkey agar showed no growth. The Gram stain revealed gram-positive budding yeast cells [Figure 1]. The isolated colonies were sub-cultured on Hi-Chrome agar (HiMedia), which, after 24 hours of incubation, showed colorless colonies [Figure 2]. *C. auris* was identified in clinical specimens using the VITEK 2 Compact System (bioMérieux, France), which is an automatic identification system, and a matrix-assisted laser desorption/ionization-time of flight (MALDI-ToF)-based automated bacterial identification system (bioMérieux, France). Antifungal susceptibility testing (AFST) for amphotericin B (AMB), fluconazole (FLU), voriconazole (VRC), caspofungin (CAS), micafungin (MFG), and flucytosine (FC) was conducted using the automated turbidimetric system Vitek 2 AST YS08 from bioMérieux (France). The drug concentration ranges for antifungal agents were as follows: Amphotericin B (AMB) ranged from 0.25 to 16 mg/ml, Caspofungin (CAS) from 0.25 to 4 mg/ml, Fluconazole (FLU) from 1 to 64 mg/ml, and Flucytosine (FC) from 1 to 64 mg/ml. Micafungin (MFG) had a range of 0.06 to 4 mg/ml, and Voriconazole (VRC) ranged from 0.125 to 16 mg/ml. Currently, there are no species-specific susceptibility breakpoints available for *Candida auris*, so the antifungal susceptibility testing (AFST) results were interpreted using the tentative breakpoints proposed by the US Centers for Disease Control and Prevention (CDC)(*Candidiasis* | *Candidiasis* | CDC, n.d.).

CASE-1

The patient came to the emergency ICU on 24th December with difficulty in breathing, falling saturation SpO₂ 88%, heart rate 77 beats/min, and blood pressure 131/66 mmHg. The patient also complained of decreased urine output. The patient is a known case of diabetes mellitus and was also on antipsychotic medications. Routine vitals were monitored, and charting was done. On the same day, the patient's blood and urine cultures were sent to the microbiology lab and pathology laboratory for various investigations. The remaining aspects of the patient's condition were managed symptomatically. Initially, the patient's blood culture showed growth of *Acinetobacter baumannii*, and antibiotics were started based on the sensitivity report. A psychiatric evaluation was also conducted. On day four, an abdominal ultrasound revealed distended bowel loops, necessitating general surgery. The patient had not passed stool for three days post-surgery and was managed accordingly. On day ten, the patient developed a fever of 100.2°F, and a blood culture confirmed the growth of *Candida auris*. The isolate was pan-resistant to antifungal drugs. Patient B.P. experienced a decline in condition, prompting the initiation of high-dose inotropes. On day 16, the patient had an episode of hypotension accompanied by bradycardia, which was followed by asystole. Cardiopulmonary resuscitation was initiated, but the patient could not be revived and was declared dead approximately 15 to 16 days after admission.

OUTCOME: cardiopulmonary arrest

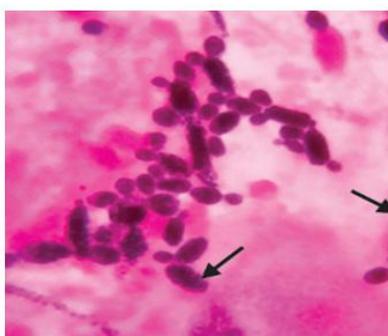


Figure 1- Gram stain image showing a budding yeast cell



Figure 2- Hi-chrome showing the white colour of *C. auris*

CASE-2

A patient was admitted to the trauma center on November 20th after falling from a height due to an electric shock. Upon arrival, he had lost consciousness and exhibited ear, nose, and throat (ENT) bleeding. The patient was managed conservatively with intravenous (IV) fluids, IV antibiotics, antiepileptics, and nutritional support. Consultations from various other departments were obtained. An MRI of the brain revealed a left frontotemporal contusion, which was treated accordingly. On the eighth day of admission, he developed a fever, and his condition deteriorated, leading to sepsis. The patient's blood cultures indicated growth of *Candida auris*, which was found to be pan-drug resistant. Unfortunately, the patient was declared dead on the twelfth day of hospitalization.

OUTCOME- Fatal

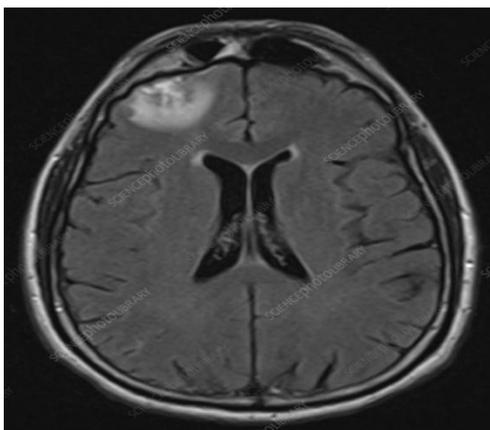


Figure 3- An MRI of the brain shows frontotemporal contusion

CASE-3

A patient was admitted to the emergency ICU on December 5th due to a coma resulting from cerebral thrombophlebitis and intracranial hypertension. The patient had a known history of hypertension. Blood and urine samples revealed impaired kidney function. Blood cultures showed positive results for fungemia. Caspofungin was prescribed for 13 days, starting with a loading dose of 70 mg, followed by 50 mg daily. The continued positivity of blood cultures prompted the addition of liposomal amphotericin B at a dosage of 350 mg daily after five days of caspofungin monotherapy. A diagnosis of *Candida auris* endocarditis was established based on the identification of vegetation on the mitral valve via transesophageal echocardiography and the persistent positivity of blood cultures. Unfortunately, the patient passed away on day 19 due to refractory intracranial hypertension.

OUTCOME: Fatal

DISCUSSION

Patients hospitalized in Indian hospitals are at very high risk of *C. auris* colonization or infection because it was recovered in the majority of ICUs studied in India, where this species represents 5.2% of all *Candida* spp. isolates (Welsh et al., 2017). A wide range of clinical symptoms has been documented, including meningitis, pericarditis, peritonitis, bloodstream infections, and urinary tract infections (Izquierdo & Santolaya, 2014). Most cases of *C. auris* invasive infection occur in critically ill patients and are associated with a mortality rate above 50% (Rudramurthy et al., 2017).

The following measures are recommended if this species is isolated in a healthcare setup. All patients colonized or infected with *C. auris* must be isolated in a single room; standard precautions, including hand hygiene, must be strictly adhered to. Handwashing should be done with soap and water to remove visible soiling, followed by alcohol hand rub. The WHO's five moments of hand hygiene should be followed to ensure proper hygiene maintenance for the patient. 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 should be carried out. All close contacts (patients in the same ICU) should be screened and isolated until three consecutive negative screens are obtained (at least 24 hours apart) (Moore et al., 2017).

Generally, three main classes of available antifungals, including azoles, polyenes, and echinocandins, have been used for the treatment of infected patients in clinics ("Clinical Profile, Antifungal Susceptibility, and Molecular Characterization of *Candida Auris* Isolated from Patients in a South Indian Surgical ICU," 2021). Different countries have reported various levels of resistance to common antifungals used against *C. auris* infection worldwide (Carty et al., 2023). Our three cases developed infections after admission to our hospital and developed fungaemia, leading to fatal outcomes.

Even after the start of antifungal drugs and other treatment options, patients did not respond and deteriorated. *C. auris* isolates of patients with candidemia in Russia were susceptible to echinocandins, whereas a high level of resistance against fluconazole and amphotericin B was seen in the majority of isolates. Further investigation into surveillance can help establish proper guidelines and protocols for managing candidemia (Barantsevich et al., 2020). Biofilms are capable of triggering antifungal resistance, thereby helping this isolate in developing persistent infection (Dominguez et al., 2019). However, echinocandins are only available intravenously and are related to higher rates of resistance by *C. auris*. Setting the MICs of antifungals against *C. auris* strains has also been a problem of concern, since elevated MICs are a problem (Spivak & Hanson, 2018). Thereby, it is equally critical to monitor the antifungal resistance in different geographical areas and implement efficient guidelines for treatment (AlJindan et al., 2020).

As multidrug-resistant *C. auris* strains are rapidly emerging, it is imperative to develop novel therapeutic strategies. The development of new antifungal agents and the combination of existing drugs might help in combating the infection (Zhang et al., 2023). Ibrexafungerp (SCY-078), a novel first-in-class antifungal agent targeting glucan synthase, was used to investigate in vitro activity against *C. auris* (Arendrup et al., 2020). Rezafungin, ibrexafungerp, and fosmanogepix are three compounds currently in late-stage clinical development (Arendrup et al., 2020). Several studies have demonstrated the effectiveness of Chlor-Clean and Haz-Tab, which are chlorine-based products with concentrations of 1000 ppm and 10,000 ppm, respectively. The contact time recommended is 3 minutes for the eradication of this isolate (Abdolrasouli et al., 2017). Vaporized hydrogen peroxide is a common method for environmental decontamination. Although the discriminating power of MALDI-TOF to finely type bacteria or yeasts is limited, it is now recognized that mass spectrometry is also able to perform strain typing and notably to classify with good reliability.

CONCLUSION

The rapid emergence of antimicrobial resistance presents a significant challenge, limiting treatment options worldwide. This situation urgently necessitates the development of new, broadly effective, and cost-efficient therapeutic strategies. Early and accurate identification of patients colonized with *C. auris* is crucial for containing its spread. Therefore, there is an urgent need for official guidelines from organizations such as WHO, ECDC, and CDC that outline proper isolation and culture techniques, as well as the best methods to prevent misidentification. *C. auris* is a significant emerging fungal pathogen that is becoming increasingly resistant to treatment, possibly due to climate change. Its ability to survive in intensive care units (ICUs) has made it a successful nosocomial infection. To combat this issue, we need to develop more antifungal agents, as options are currently limited. Rapid diagnostics, particularly point-of-care tests, would facilitate timely preventive measures and more efficient screening. Some healthcare facilities have struggled to contain outbreaks after admitting infected patients, highlighting the importance of improving infection control measures to prevent future occurrences.

Ethics Statement

The study was conducted in accordance with institutional ethical standards. Ethical approval was waived due to the retrospective, anonymized nature of the case series.

Informed Consent

Informed consent was waived as no patient-identifiable information was disclosed.

Declaration:

Conflicts of interests: The authors declare no conflicts of interest.

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