Editorial

The Emerging Rise in *Candida auris*: A Global Threat

Aqsa Aslam

The emerging rise in *Candida auris* infections is a potential threat worldwide and one of the greatest challenges in the treatment & prevention of infectious diseases. This is attributed to the multidrug resistance of *Candida auris*, difficulty in laboratory identification of the organism and outbreaks of the infection in healthcare settings.[1] *Candida auris* is rapidly transmitted from person to person. The mortality rate of candidemia caused by *Candida auris* is 60%.[2]

The fungus was first isolated in Japan in 2009 from the ear of a patient.[3] After that *Candida auris* was identified in 15 patients with otitis media in South Korea.[4] Bloodstream infection caused by *Candida auris* was reported in South Korea in 2011.[5] *Candida auris* has also been reported from United States, Canada, Germany, India, South Korea, Israel, Japan, Kenya, Pakistan, Norway, Spain, South Africa, the United Kingdom, Kuwait, Venezuela and Oman.[6] However, only six countries of the Middle East have documented *Candida auris* infections. These include Oman, Kuwait, KSA, Israel, UAE and Iran.[7]

Recently, the Centers for Disease Control & Prevention (CDC) and the European Centre for Disease Prevention & Control (ECDC) have warned about the rising burden of *Candida auris* infections. By September 2017, 127 cases were reported to the CDC from 10 states. These strains were similar on whole-genome sequencing (WGS) analysis.[9]

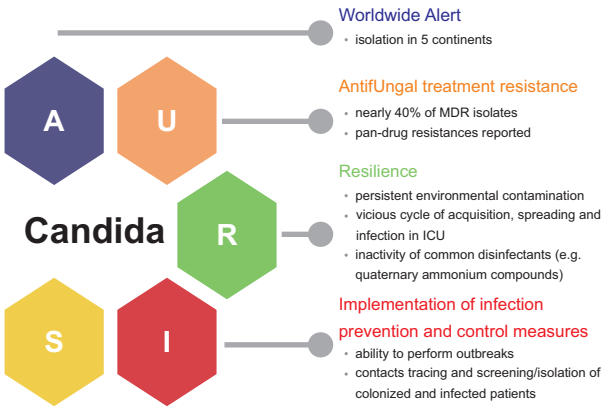

Figure 1: "Major Issues Related to *Candida auris*"[8]

Sharif Medical and Dental College
Sharif Medical City Road, Off Raiwind Road, Jati Umra, Lahore 54000, Pakistan.

Correspondence: Dr. Aqsa Aslam
Assistant Professor Department of Pathology
Sharif Medical & Dental College, Lahore
E-mail: aksaaslam@hotmail.com
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Candida auris causes invasive disease in hospitals across the globe.[10] The patients usually have undergone surgical procedures, vascular catheterization, mechanical ventilation and gastrostomy tube placement. Like other candida species, *Candida auris* causes infections by producing biofilm on indwelling medical devices.[11] *Candida auris* causes several invasive fungal infections, the most important of which is candidemia. It also causes pericarditis and respiratory tract & urinary tract infections.[12] This yeast can be recovered from several human specimens including sterile body fluids, ears, wounds and mucocutaneous swabs.[8] *Candida auris* can colonize many sites of the body such as nares, axilla, groin and rectum. The eradication is difficult even after treatment.[13] Individuals having contact with patients harboring *Candida auris* or their environment are at risk of colonization.[14] The time required for acquiring *Candida auris* is only ≥4 hours.[13] It is markedly resistant to a variety of disinfectants which explains the nosocomial transmission of the organism.[15] It survives on the surface of medical devices and hospital rooms.[11]

The rise in the prevalence of *Candida auris* is due to the increasing use of prophylactic antifungal drugs. Previously, the majority of the cases of invasive candidiasis were caused by *Candida albicans* and fluconazole was given for treatment. With the emergence of multidrug-resistant non-albican species, fluconazole cannot be the drug of choice.[16]

Neutrophils are an important defense mechanism in invasive candidiasis. They phagocytose the fungi, form neutrophil extracellular trap (NET) and deliver the antimicrobial contents. But neutrophils fail to phagocytose *Candida auris*.[11]

Candida auris produces white or cream-colored colonies on Sabouraud dextrose agar (SDA) and pink or beige colonies on CHROMagar. It forms oval to elongated budding yeast cells without pseudohyphae on cornmeal or rice Tween 80 agar. It can grow both at 37°C and 42°C. It can assimilate gluconate, succinate and N-acetylglucosamine.[17] However, it cannot grow in 0.01% cycloheximide.[12] In comparison, *Candida haemulonii* and *Candida duobushaemulonii* form

pseudohyphae, cannot grow at 42°C and do not assimilate the same sugars.[18] Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is the diagnostic method for detecting *Candida auris*, provided that it is included in the reference profile database.[19]

The outbreaks of infections are difficult to control due to several reasons. It may be misdiagnosed as *Candida haemulonii* in laboratories where molecular biology or MALDI-TOF techniques are not performed. Secondly, the eradication of the outbreaks from the affected areas is difficult. The organism has a rapid patient to patient transmission. The multidrug resistance of the organism limits the treatment options. Most of the strains of *Candida auris* exhibit intrinsic resistance to fluconazole.[20] Initial therapy with echinocandins is recommended. Patients should be monitored for antifungal resistance. Treatment should not be considered in cases of colonization without active disease. The patients with *Candida auris* infection or colonization had a history of broad-spectrum antibiotics and/or antifungals use. The antimicrobial stewardship policies should be implemented to reduce the unnecessary use of antibiotics. These policies can also help in proper diagnosis and management of these infections & their prevention.[19]

The impact of epidemics or pandemics of *Candida auris* in the future is difficult to determine but it depends on the measures taken at this point of time to manage this situation.[1] There is a high likelihood of transmission of *Candida auris* from the patient to the healthcare workers. The organism colonizes the skin or mucous membranes of the patients. The organism has also been isolated from mattresses, furniture, sinks and medical equipment.[9] The CDC emphasizes that adequate infection control measures should be reinforced in hospital settings to prevent these infections. These measures include adherence to good hand hygiene, contact precautions, isolation of infected patients, proper cleaning and disinfection of the room. Hydrogen peroxide and disinfectants containing chlorine can kill *Candida auris*. However, quaternary ammonium compounds are not active against *Candida auris*. Chlorhexidine and iodine compounds are also effective against *Candida auris*.[21] A study conducted by Schelenz et al. reported that despite the daily use of chlorhexidine washes in an outbreak, the transmission of *Candida auris* continued.[13]

In an experimental study, a vaccine developed against *Candida albicans* (NDV-3A) protected mice from *Candida auris* infection. Since the safety and effectiveness of the vaccine in humans against *Candida albicans* is proven, the vaccine should be tested against *Candida auris* in future clinical trials.[22]

In Pakistan, *Candida auris* outbreak occurred in 2014 in Aga Khan University Hospital, Karachi. The fungus was identified as *Saccharomyces cerevisiae.* But it had an unusual antifungal susceptibility pattern. The strains were reported as *Candida auris* by the CDC.[2]

A retrospective study was conducted by Sayeed et al. at Aga Khan University Hospital from September 2014 to March 2017 in which *Candida auris* was isolated from

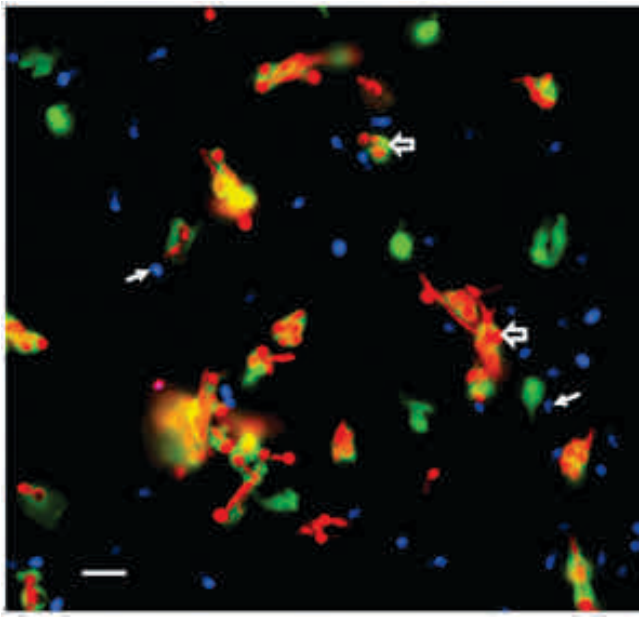

Figure 2: "Human Neutrophils Fail to Engage *Candida auris* Calcein acetoxymethyl (AM) labeled human neutrophils (green) were cocultured with red fluorescent protein-tagged *Candida albicans* (red) and calcofluor white-stained *Candida auris* (blue) for 30 min. Neutrophils preferentially engaged *Candida albicans*, ignoring *Candida auris*. Open arrows point to neutrophils phagocytosing *Candida albicans*. Closed arrows show *Candida auris* cells. Few neutrophils engage *Candida auris* in the presence or absence of *Candida albicans*. Measurement bar represents 10 µm"[11]

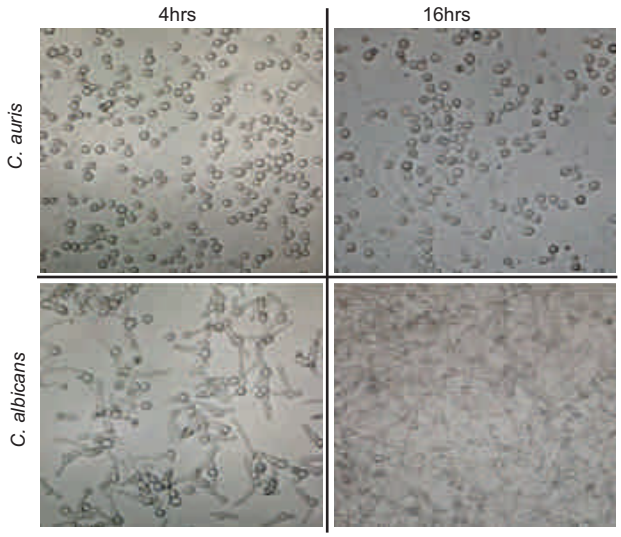

Figure 3: "Growth of *Candida auris* in Comparison to *Candida albicans* at Biofilm-Forming Condition at 4 and 16 Hours. *Candida* Isolates were Cultured at 37°C in 125 ml Corning Culture Flasks"[6]

Table 1: "Key Points for *Candida auris* Prevention and Control by the European Centre for Diseases Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC)"[23]

ECDC	CDC
Correct identification (MALDI-TOF; DNA sequencing of the D1/D2 domain): Clinicians and microbiologists alertness; Notification and retrospective case-finding	Correct identification (MALDI-TOF; molecular methods) Confirmed isolates of *C. auris* should be reported to local and state public health officials and to CDC
Good standard infection control measures (including environmental cleaning, reprocessing of medical devices and patient isolation) and prompt notification	Infection control measures: • Placing the patient with *C. auris* in a single-patient room and using contact precautions • Emphasizing adherence to hand hygiene • Cleaning and disinfecting the patient care environment (daily and terminal clearing) with recommended products • Screening contacts of newly identified case patients to identify *C. auris* colorization
Early identification of carriers by using active surveillance cultures (sites considered for sampling include nose/throat, axilla, groin, rectum, insertion sites of venous catheters; clinical samples such as urine, faeces, wound drain fluid, and respiratory specimens)	Screening should be performed to identify colonization among potentially epidemiologically linked patients, including: • Current roommates • Roommates at the current or other facilities in the prior month (even if they have been discharged from the facility) Screening for *C. auris* should be done using a composite swab of the patient's axilla and groin (sites of consistent colonization). Patients have also been found to be colorized with *C. auris* in nose, external ear canals, oropharynx, urine, wounds, and rectum.
Establish the source of the outbreak (epidemiological investigation, cross-sectional patient screening and environmental sampling); prevention of inter-hospital and cross-border transmission Enhanced control measures to contain outbreaks (such as contact precautions, single room isolation or patient cohorting, and dedicated nursing staff for colorized or infected patients)	All laboratories, especially laboratories serving healthcare facilities where cases of *C. auris* have been detected, should: • Review past microbiology records to identify cases of confirmed or suspected *C. auris* • Conduct prospective surveillance to identify *C. auris* cases in the future •Consider screening close contacts of patients with *C. auris* for presence of colonization
Education and practice audits (for healthcare workers and contacts)	Education of all healthcare personnel, including staff working with environmental cleaning services about *C. auris* and need for appropriate precautions; Monitor adherence to infection control practices
Antifungal stewardship	Antibiotic and antifungal stewardship

92 hospitalized patients. Of the 92 patients, 65(70.7%) had an infection while 27(29.3%) had colonization with *Candida auris*. Out of 65 infected patients, 38 had bloodstream infections while 27 had other infections. All the strains showed fluconazole resistance. Voriconazole and amphotericin resistance was seen in 28.5% and 7.9% patients, respectively. The mortality rate was 42.4%, with higher mortality in candidemia patients.[24] It is the need of time to raise awareness in healthcare facilities regarding *Candida auris*. So that they establish protocols for its laboratory diagnosis and implement infection control measures.[25]

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