Research Journal of Recent Sciences ISSN 2277-2502
Vol. **12(1),** 27-32, April **(2023)** *Res. J. Recent Sci.*

Review Paper

Candida auris- threat to human healthcare facilities

Sahana Ghosh
Faculty of Department of Microbiology, Vijaygarh Jyotish Ray College (affiliated to the University of Calcutta), Kolkata, West Bengal, India
sahanaghosh2102@gmail.com

Available online at: www.isca.in, www.isca.me
Received 16th February 2022, revised 18th November 2022, accepted 4th March 2023

Abstract

Candida auris is reported first as an emerging life threatening multidrug resistant pathogen in Japan, in 2009. Outbreak of this pathogen is usually nosocomial. Spread of this infection is of high concern as cases of transmission are found to take place despite implementation of enhanced infection prevention and control (IPC) measures. Different clinical manifestations of this multidrug resistant pathogen is from bloodstream infections (BSIs), deep-seated candidiasis, intra-abdominal candidiasis, to superficial infections occurring in patients, who are undergoing treatment for long period, specially to those who have lines or tubes entering their body, have central venous catheter or previously received antibiotics or antifungal medications. Epidemiological studies revealed sporadic distribution of C. auris in many countries worldwide. Evidences revealed about the genes and proteins involved in virulence and multidrug resistance in C. auris. Techniques to restrict the spread and possible controlling mechanisms required are recommended by ECDC and CDC. However, hospitals, even in developed countries also, are still not satisfactorily equipped to combat possible outbreak, because antifungal repertoire against C. auris is very limited. Therefore, further investigations in the field of disease epidemiology, therapeutics, immunology as well as molecular biology of C. auris are warranted.

Keywords: *C. auris*, multidrug resistance, virulence factors, nosocomial infection, disease prevention.

Introduction

Candida auris is a fungus belonging to *Debaryomycetaceae* family, class *Saccharomycetes*, Order *Saccharomycetales* and genus *Candida.* It was reported first as an emerging life threatening multidrug resistant pathogen in 2009, in Japan, from the external ear canal discharge of a patient[1]. The outbreak of this superbug is creating a near-future possibility of threat of catastrophic dimension in the human healthcare facilities if proper measures to be taken are not made available soon to medical practitioners world over. Outbreak of this pathogen has been reported to be through nosocomial transmission of the patients in ICU. Spread of this infection is of high concern as cases of transmission are found to take place despite implementation of enhanced infection prevention and control (IPC) measures[2]. Different clinical manifestations of this multidrug resistant pathogen is from bloodstream infections (BSIs), deep-seated candidiasis, intra-abdominal candidiasis, to superficial infections[3-5]. It is mainly a hospital-associated infection involving seriously ill patients, who are undergoing treatment for long period, especially to those who have lines or tubes entering their body, have central venous catheter or previously received antibiotics or antifungal medications [Centers for Disease Control and Prevention; CDC 24/7: Saving Lives, Protecting People; *Candida auris*]. Isolates of *C. auris* have been recovered from typically sterile body fluids, respiratory sections, bile, urine, tissues, wounds and mucocutaneous swabs[6-11]. Studies showed that it is unique for a fungal pathogen and surmise that it is a skin commensal rather than gastrointestinal microbiota[12,13]. Pathogen becomes resistant to various drugs due to excessive use of broad-spectrum antibiotics[14] and is spreading worldwide rapidly across five continents. Reports of outbreak are mainly coming from America and European countries[15,2,16].

Epidemiology

The ubiquitousness and the epidemiology of *C. auris* remains unresolved till now. Treatment of Candida is limited due to unavailability of conventional diagnostic tools[12,13]. Study revealed that a single *C. auris* was isolated from Pakistan in the year 2008[12,13]. In the year 2011, it had been reported that highly multidrug resistant *C. auris* varieties caused invasive bloodstream fungemia in three patients[6]. Phylogenetic analyses stipulated that Candida species showed rapport to unusual species[1] such as *C. haemulonii* and *C. pseudo haemulonii*. Genome sequencing and analyses exhibited that in South Korea[17], 15 patients were affected by chronicotitis which were distinguished to be contaminated via atypical and clonally allied yeast isolates of *C. auris*[18]. *C. auris* infections have been documented midst many countries, together with India[10,19-21]. Approximate length of *C. auris* haploid genome is 12.5 Mb having nearly 45% of guanine-cytosine residues[22-24]. Beside, multiple transporter genes and protein kinases have been identified which accelerate the accession of drug resistance[23]. Studies in India revealed that 19 out of 27 patients were infected

with candidemia cases in an ICU. The ubiquitousness of the infection is about 3.2% in private and 8.2% in public hospitals[10]. Epidemiological studies have reported worldwide spread of *C. auris* (Figure-1).

Countries like Austria, Belgium, Iran, Malaysia, the Netherlands, Norway, Switzerland, Taiwan, and the United Arab Emirates reported single cases.

From Australia, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, the United Kingdom, the United States (primarily from the New York, New Jersey, and the Chicago) and Venezuela multiple cases reported. In some of these countries, substantial transference has been documented.

Other countries not focused on this map may also have undetected *C. auris* cases.

Clinical Characteristics

C. auris is responsible for causing various clinical conditions like infections in blood, infection occurring in urinary tract, otitis, infections from surgical wounds, skin abscesses (like catheter insertion), inflammatory cardiomyopathy, meningococcal meningitis, bone infections and many more[26,27]. Study showed that risk factors associated are because of previous exposure to broad-spectrum antibiotics and fungicides, diabetes mellitus, abdominal and vascular surgery, post-operative drain placement, chronic renal disease, chemotherapy, blood transfusions, hemodialysis, total parenteral nutrition, immunosuppressive state[28] and neutropenia[29], and duration of stay in ICU[19,30].

Virulence and resistance factors

Several lines of evidences revealed the genes and proteins involved in virulence and multidrug resistance in *C. auris*, which are summarized in Table-1.

Table-1: Factors showing virulence and resistance properties of *C. auris*[14].

Virulence genes of *C. auris* that encodes: ➢ Hemolysin, secreted aspartyl proteinases, secreted lipases, phosphatases, mannosyltransferases, phospholipase, integrins, adhesins, Zn(II) 2 cys 6 transcription factor (strain-specific degree of activity)
Resistance genes: ➢ Resistance against azoles ➢ Transport proteins and efflux pumps ➢ ERG 11 mutations and ➢ ERG 11 over expression
Resistance against Echinocandin ➢ FKS1/2 (encodes 1,3-beta-glucan synthase, echinocandin drug target)
For adheration to exterior and plastic materials (e.g., catheters)
For the development of Biofilm
Cellular morphology (aggregating and non-aggregating forms)
For the emergence of Rudimentary pseudohyphae

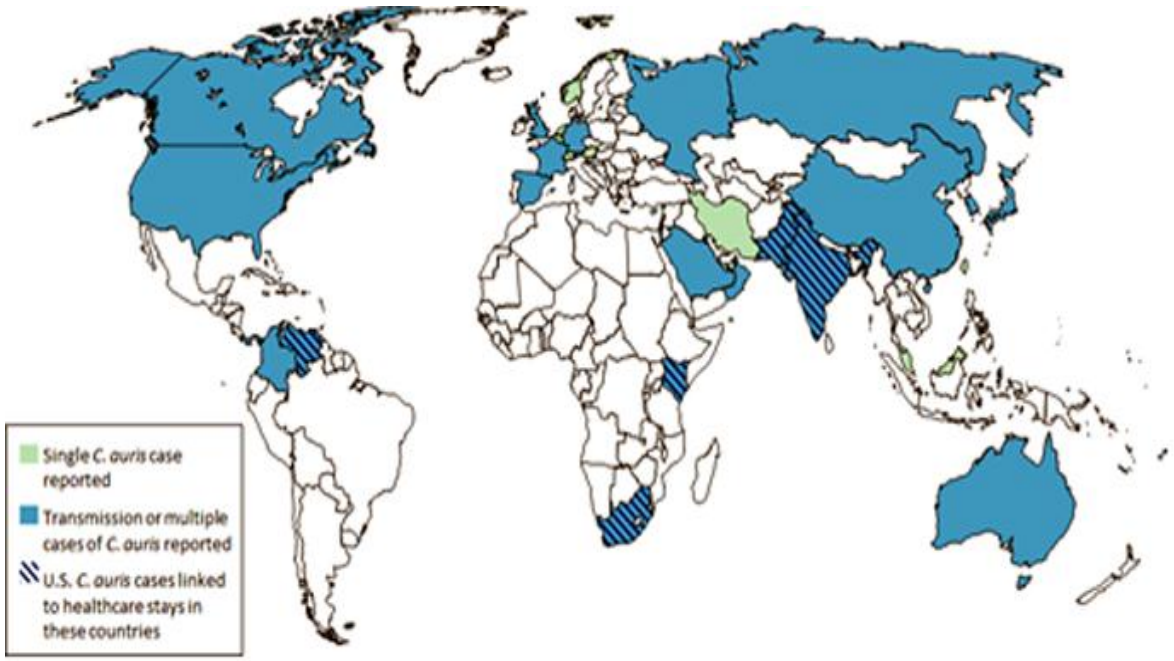

Figure-1: Countries from where *C. auris* cases have been documented, as of February 28, 2019[25].

Resistance properties of *C. auris*

Multiple drug resistance properties and partial mechanisms of drug resistance in *C. auris* have been elucidated so far which are summarized in Table-2. i. A notable amount of genes take part in metabolism which are responsible for pathogenicity thereby adapting them to divergent environments[15]. ii They are found to be resistant to cationic surface-active products and quaternary compounds. Sporicidal activity of disinfectants, products of hydrogen peroxide have the ability to clean the surfaces resulting in decrease in the bacterial population. iii. It has been suggested to decontaminate the patients' belongings with ultraviolet light, chlorine based detergents or with hydrogen peroxide vapour[31,25]. iv. Research activities of Sherry et al. suggested that *C. auris* have the ability to form antifungal-resistant biofilms, against all three main classes of antifungals[25], which were found to be resistant to chlorhexidine and hydrogen peroxide. v. Kean et al. explored the genes that are responsible for causing *C. auris* to be resistant within the biofilm. vi. Transcriptomic analyses of biofilms showed to manifest phase- and antifungal class-dependent resistance profiles. Differential expression analysis in biofilm formation and planktonic cells, demonstrated that 791 and 464 genes were upregulated[32]. vii. Study revealed that FKS1 sequencing of *C. auris* isolates which depicted that an S639F mutation in FKS1 hot spot region 1 made the isolates resistant to all tested echinocandins (MIC ≥ 4 mg/liter). viii. Antifungal susceptibility test with caspofungin was utilized as all *FKS1* WT isolates manifested an Eagle effect (also known as the paradoxical growth effect)[33], exhibiting high MIC against major antifungal drugs like azoles, polyenes, and echinocandins[12,13]. ix. Recent reports depicted high MICs to amphotericin B,voriconazole, and caspofungin[34]. 45% of *C. auris* isolates showed low MICs of fluconazole in Delhi, India[35]. x. Furthermore, it has been suggested that multidrug resistance property of this pathogen might have been due to a large portion of genome encoding the ATP-binding cassette (ABC), major facilitator superfamily (MFS) transporter families with drug transporters[28,29]. xi. Resistance against azoles is attained due to the ABC-type efflux activity by Rhodamine 6G transport[36]. xii. *C. auris* is thermotolerant, salt tolerant, can grow at 37^0C and exhibit viability upto 42^0C, have the ability to form large aggregate which is difficult to disperse, thereby helping many strains to persist in the hospitals[37,1].

Table-2: For most common antifungal drugs,minimum inhibitory concentration (MIC) range and tentative MIC breakpoints of *C. auris*.

Drugs	MIC range (mcg/ml)	Tentative MIC breakpoints (mcg/ml)
Triazoles		
Fluconazole	0.12 to > 64	≥ 32
Voriconazole (and other 2° generation azoles)	0.032–16	N/A
Polyenes		
Amphotericine B	0.06–8	≥ 2
Echinocandins		
Anidulafungin	0.015–16	≥ 4
Caspofungin	0.03–16	≥ 2
Micafungin	0.015–8	≥ 4

Prevention and Control

Prevention and controlling measures need to be taken due to sporadic outbreak and resistance properties of *C. auris*. Techniques needed to be adopted to restrict the spread and possible controlling mechanisms required are listed in the table given by ECDC and CDC (Table-3).

Table-3: Key points of prevention and controlling of *C. auris* by the European Centre for Diseases Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC)[14].

ECDC	CDC
Correct identification of infected patients by using techniques like Maldi-Tof; Dna sequencing of the D1/D2 domain, awareness need to be spread and clinicians and microbiologists are to be vigilant.	Accurate identification need to be made by utilizing the techniques such as MALDI-TOF and other molecular methods. Confirmed cases of *C. auris* need to be isolated, must be informed to health centers and CDC
Cleaning environment, medical devices need to be reprocessed and isolation of patients and notification need to be taken promptly	Infection control measures: • *C. auris* infected patients to be isolated in a single-room and using contact precautions • Emphasizing on hand hygiene • Patient care environment to be cleaned and disinfected • Newly identified patients need to be screened to detect*C. auris* colonization

Identifying the carriers by using active surveillance cultures like samples of nose, throat, axilla, groin, rectum, catheters insertion sites	Screening of current roommates should be performed Screening for *C. auris* should be done using a composite swab of the patient's axilla and groin. Patients infected with *C. auris* in nose, external ear canals, oropharynx, urine, wounds, and rectum have been identified
Finding the outbreak source, cross-sectional screening of patients, environmental sampling, preventing the transmission of inter-hospital and cross-border	Laboratories where cases of *C. auris* have been detected, should: • Go through the previous records to identify cases of confirmed or suspected *C. auris* • Conduct probable surveillance to figure out the cases • Screenpeople having close contacts with patients having*C. auris*
Increasing the measures to control outbreaks by isolating the patients in a single room, taking dedicated and subject experienced nurse staff for handling infected patients	All healthcare personnel should be educated about *C.auris* and appropriate precautions need to be taken like environmental cleaning
Educating healthcare workers and contacts need to be increased so that they get access to knowledge	Antibiotic and antifungal stewardship
Antifungal stewardship	

Conclusion

Antifungal repertoire for systemic treatment is limited for patients still today owing to toxicity concerns. In this present scenario, along with frequent reports of multidrug resistant bacterial varieties, fungal resistance is also emerging as a potent threat. Hospital acquired fungal infections caused by deadly candida sp. like *C. auris* is one of the newest and rapidly evolving risk. Studies reported so far from many places across the globe have revealed the threatening level of virulence and pathogenesis of this microorganism, especially in patients. Some information regarding its high level of drug resistance are also available. However, hospitals, even in developed countries also, are still not satisfactorily equipped to combat possible outbreak, because antifungal repertoire against *C. auris* is very limited. Therefore, further investigations in the field of disease epidemiology, therapeutics, immunology as well as molecular biology of *C. auris* are warranted. *C. auris* is of special importance in Indian medical field because Indian hospitals serve a huge number of patients, where an outbreak is highly difficult to combat with inadequate surveillance and treatment measures.

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