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CANDIDA AURIS INFECTION: HOW PREPARED IS NIGERIA FOR THIS EMERGING FUNGAL AGENT?

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ABSTRACT

Reports from Asia and other parts of the world have demonstrated that the incidence of *Candida auris* infection is on the rise. *Candida auris* is a fungal pathogen causing a wide variety of infections affecting people of all age groups. *Candida auris* was first described in 2009 and has since emerged as an important cause of invasive fungal infection, most importantly healthcare-associated candidaemia. Large outbreaks have been reported worldwide, with therapeutic failure and associated high mortality rates recorded.

The emergence and spread of *C. auris* raises public health concerns because of some characteristics of this pathogen. First it is resistant to many antifungal agents making this infection very difficult to treat. It is also associated with horizontal transmission in health care settings causing outbreaks among hospitalized individuals with high mortality rates. Furthermore, identification of *C auris* is a challenge. Routine identification methods usually misidentify the organism as other yeasts especially *Candida haemulonii*.

This review discusses the current knowledge on the epidemiology, treatment and control of this infection. The urgent need for the stakeholders in Nigerian tertiary hospitals to set machinery in motion for prompt diagnosis, management and prevention of transmission of this infection are also discussed.

INFECTION À CANDIDA AURIS: COMMENT LE NIGERIA EST-IL PRÉPARÉ POUR CET AGENT FONGIQUE ÉMERGENT?

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ABSTRAIT

Des rapports en provenance d'Asie et d'autres parties du monde ont démontré que l'incidence de l'infection à Candida auris est en augmentation. Candida auris est un pathogène fongique causant une grande variété d'infections affectant les personnes de tous les groupes d'âge. Candida auris a été décrit pour la première fois en 2009 et est depuis apparu comme une cause importante d'infection fongique invasive, surtout la candidémie associée aux soins de santé. De grandes épidémies ont été signalées dans le monde entier, avec des échecs thérapeutiques et des taux de mortalité élevés associés enregistrés.

L'émergence et la propagation de C. auris soulèvent des préoccupations en matière de santé publique en raison de certaines caractéristiques de ce pathogène. D'abord, il est résistant à de nombreux agents antifongiques rendant cette infection très difficile à traiter. Il est également associé à la transmission horizontale dans les milieux de soins de santé, ce qui provoque des éclosions parmi les personnes hospitalisées avec des taux de mortalité élevés. De plus, l'identification de C auris est un défi. Les méthodes d'identification de routine confondent généralement l'organisme avec d'autres levures, en particulier Candida haemulonii.

Cette revue discute les connaissances actuelles sur l'épidémiologie, le traitement et le contrôle de cette infection. Le besoin urgent pour les parties prenantes des hôpitaux tertiaires du Nigeria de mettre en place un système de diagnostic rapide, de prise en charge et de prévention de la transmission de cette infection est également discuté.

INTRODUCTION

Candidaemia and candidiasis are usually caused by *Candida albicans* but infections due to non albicans *Candida* species have been on the increase globally. (1) Cases of invasive non albicans candidiasis have been reported from many parts of the world. Among the non albicans *Candida* species; *C. glabrata* and *C. tropicalis* have emerged as important opportunistic pathogens with other species being reported to a lesser degree.

In 2009, a novel yeast species belonging to the genus *Candida* was isolated from the external ear canal of a patient admitted in a Japanese hospital. (2) DNA analysis revealed this new species to be closely related *Candida ruelliae* and *Candida haemulonii* in the Metschnikowiaceae clade. It was thereafter named as *C. auris* based on its first isolation from an ear infection. (2)

Candida auris is an unusual *Candida* species first found in human ear specimens. It is capable of hospital acquired transmission leading to large outbreak in health care settings. (3) It has emerged as a significant pathogen in hospitals and accounts for 8.6% to 30% of cases of candidaemia in a recent report. (4)

Contaminated surfaces was thought to be the source of dissemination of *C. auris*, however, urogenital colonization from an indwelling urinary catheter could also result in dissemination to the blood stream causing fungemia. (5, 6)

EPIDEMIOLOGY

Candida auris has become an important nosocomial pathogen with widespread dissemination across several Asian countries and other parts of the world. (7) The actual global picture remains unclear as the current commercial methods of laboratory diagnosis misidentify *C. auris* (8)

Since it was first reported in Japan in 2009, *C auris* has been reported in many other regions of the world. (2) In South Korea, it was isolated in fifteen cases of chronic otitis media and subsequently in three patients with blood stream infections across three different hospitals. (9) Candidaemia caused by *C. auris* has also been reported in India and South Africa, with an estimated prevalence of 0.3%. (10) (6) The first cases in the United Kingdom were recorded in 2013 from blood cultures, thereafter there have been many others documented including outbreaks in 2013 and 2015-2016. (3, 7) In the United States, *C. auris* has been identified from over 122 patients, 77 clinical cases and 45 patient contacts. Majority of the cases were in New York. (11) Whole-genome sequencing of *C. auris* isolates has shown, clustering into four distinct clades. (11) Studies have found that isolates from within each geographical region are highly related to one another whereas isolates from different regions did not exhibit such relatedness. (11, 12) These suggest independent emergence of *C. auris* within geographical regions followed by local transmission. (11, 12) This geographically specific clustering of C *auris* has also been demonstrated in a study involving samples from the India, South Africa, Japan, Korea and Brazil. (13)

PATHOGENESIS

C. auris has an innate pliability for survival and persistence in the hospital environment; it is able to rapidly colonize patients' skin and is highly transmissible within the healthcare setting. (3). This has led to serious and protracted outbreaks. *C. auris* does not produce hyphae and produces only rudimentary pseudohyphae, however many strains are highly pathogenic with some as pathogenic as *C albicans.* (7), (14) Various virulence factors are responsible for the ability of *C. auris* to easily survive and persist in infection sites. Phospholipases are extracellular hydrolytic enzymes which help in adherence and invasion of host cells and this has been demonstrated in *C. auris.* (14, 15) *C. auris* also produces heamolysin leading to invasive disease and widespread infection. (15) Proteinase activity has also been demonstrated in *C. auris* and is said to be in higher proportion than phospholipase production. (15) (14)

Some isolates of *C. auris* have been noted to form large aggregates as a result of failure of budding yeast to separate. This observation was found in cases of lethal infection and it is thought that aggregation might be a mode of immune evasion and tissue persistence. (7) (16)

Earlier studies had also reported the lack of biofilm production by *C. auris* compared to its counterpart *C. haemulonii*. (17) Subsequent researches have however demonstrated that *C. auris* is able to differentially adhere to polymeric surfaces, form biofilms, and resist antifungal agents. (18) These biofilms are, however, much thinner than those formed by *C. albicans* and have a limited amount of extracellular matrix. (14) *C. auris* is also able to grow at high temperatures of 37°C–42°C and exhibit lethality and tissue invasion close to that of *C. albicans*, the most pathogenic *Candida* species. (16)

RISK FACTORS

Individuals at extreme ages have been noted to be at high risk of infection. (9) Presence of foreign bodies such as central venous catheters, urinary catheters and mechanical ventilation also increase the risk of infection. (9) (19) (6) Concomitant use of broad-spectrum antibiotics and use of antifungals puts the patient at higher risk. (6, 13) A case series involving many countries has found intensive care stay to be a major risk factor for *C. auris* infections which is similar to other studies. (3, 13, 19)

Comorbidities and immunosuppressive conditions such as diabetes mellitus, chronic kidney disease, cancer chemotherapy, hematologic malignancies, and bone marrow transplantation have also been identified. (1) (20) Additional risk factors are erythrocyte transfusion, parenteral nutrition,

abdominal surgery, hemodialysis, pancreatitis and HIV infection. (9) (13) (19) (20)
Neutropenia does not appear to carry appreciable risk according to available reports. (9), (1)
A study found longer ICU stay, underlying respiratory disease, vascular surgery, medical intervention and exposure to antifungals as the major risk factors for acquiring *C. auris* infection. (21)

CLINICAL CONDITIONS
C. auris is an emerging fungal pathogen that can cause a wide range of human infections especially in intensive care settings (22), (4) The clinical spectrum of C. *auris* infections has expanded from minor cases of superficial infections to highly invasive bloodstream infections. (8) It is a source of multi-resistant health-care associated infections with a high potential for horizontal transmission in the hospital setting. (23) Many studies including that by Schelenz et al have demonstrated such transmission in hospitalized patients. (3) *Candida auris* is a recognized cause of chronic otitis media, wound infections, including diabetic foot. (22) (7). The occurrence of candidaemia due to *C auris* appears to be on the increase and is associated with high mortality of up to 50%. (3) (7) (11) *C. auris* accounted for 30% of the annual candidaemia cases in a tertiary care general hospital; most of the patients had persistent candidaemia with overall mortality rates of 30- 50%. (6) *C auris* had also been reported as a cause of bronchopneumonia. (22), (11) Other sites where *C auris* has been cultured are urine, bile fluid, bone and jejunum. (11)

LABORATORY DIAGNOSIS
Specimens for laboratory diagnosis depend on clinical presentation and include blood, sputum, swabs, urine and others. On Sabouraud dextrose agar (SDA), colonies of *C. auris* are white to cream colored and smooth. (9), (4) Microscopic examination shows ovoid to globose budding yeast cells in singles or pairs. (4) *C. auris* does not form chlamydoconidia or pseudohyphae on cornmeal agar. (4) (14) It failed to form Chlamydospores even after 3 days of growth on Cornmeal agar at 30°C. (6) It grows well at 37 and up to 42°C but does not grow at 45°C. (9) (6) No growth has been observed on cycloheximide-containing medium. (9) Urease test and nitrate assimilation test are both negative in *C. auris.* (9) In contrast to *C. auris, C. haemulonii* and *C. duobushaemulonii* isolates produce pseudohyphae and do not grow at 42°C. (4)
Assimilation of N-acetylglucosamine (NAG) is quite variable and therefore not valid in differentiating *C. auris* from *C. pseudohaemulonii.* (4) (6) It appears pink on CHROM-agar *Candida* medium and grows at 37°C and 42°C. (6)

Although *C. auris* is close phylogenetically to *Candida haemulonii* and *Candida ruelliae* in the Metschnikowiaceae clade analyses of the 26S rDNA D1/D2 domain, nuclear ribosomal DNA ITS region sequences, and also chemotaxonomic studies have indicated that it represents a new species. The taxonomic description of *Candida auris* sp. nov. was proposed in 2009. (2)
Unfortunately, the usual phenotypic tests are unable to correctly identify *C auris* which is misidentified as one of the closely related Candida species especially *C haemulonii*.
The Vitek 2 system is unable to differentiate between isolates of *C. auris* and those of *C. haemulonii* and *Candida pseudohaemulonii* identifying them as *C. haemulonii* or *C. famata.* (9), (6), (10)
In addition, the API 20C system, identified isolates of *C. auris* as *Rhodotorula glutinis,* or *C. sake* while *C. haemulonii* and *C. pseudohaemulonii* were identified as *Kodamaea ohmeri*.(9) (6)
Currently, the reliable methods for definitive identification of *C. auris* are molecular based methods such as PCR, sequencing analysis, amplified fragment length polymorphism (AFLP) fingerprinting and MALDI-TOF biotyping. (1, 3, 13) Internal transcribed spacer (ITS) region sequencing is used to confirm the identity of suspected isolates as *C. auris*. (6), (1), (3), (4)

Matrix assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) can be used to identify related species of Candida. (4) AFLP has been shown to reliably distinguish *C. auris* from other closely related species such as *C. haemulonii, C. pseudohaemulonii and C. duobushaemulonii.* (3) In addition, REAG-N can be used for epidemiologic typing of *C. pseudohaemulonii* and *C. auris* isolates. (17)
A cheap method was devised by Kumar et al for identifying *C. auris* among isolates identified by VITEK2 as members of C. *haemulonii* complex. CHROMagar *Candida* medium is supplemented with Pal's agar and on this medium *C. auris* strains show confluent growth of white to cream colored smooth colonies both at 37°C and 42°C without pseudohyphae production. On the contrary, *C. haemulonii* complex isolates show poor growth of smooth, light-pink colonies later becoming semi-confluent with pseudohyphae production. (24)

ANTIFUNGAL RESISTANCE
C. auris has a phylogenetic relationship with *Candida krusei*, *C. haemulonii*, and *C. lusitaniae*. These species are known to have either intrinsic or inducible resistance to antifungal agents such as fluconazole and amphotericin B. (12) There are at present no epidemiological cutoff values (ECVs) or clinical

breakpoints defined for *C. auris*, thus non species-specific breakpoints are usually used. (25)

C. auris isolates are resistant to fluconazole with high MICs observed in virtually all reports. (6), (1) (10) (4) Among the other azoles, isavuconazole, posaconazole, itraconazole and voriconazole, potent activity against *C. auris* has been demonstrated. (1),(26) The results are however inconsistent as variable results have been observed depending on the study. One study found posaconazole to have the most potent activity in vitro followed by isavuconazole then itraconazole. (25) Reduced susceptibility voriconazole has been demonstrated in some isolates but with excellent activity of isavuconazole and posaconzole. (10), (4) In contrast, another study observed resistance to itraconazole but susceptibility to voriconazole. (15) Flucytosine also shows excellent in vitro activity. (6)

In most investigations, Amphotericin B showed excellent activity against *C auris* athough a few cases of resistance have been observed. (1), (6), (10), (15), (25)

The echinocandins, caspofungin, anidulafungin and micafungin, have excellent activity against the organism.(1, 6, 10) *C. auris* resistant to all classes of antifungals including echinocandin has been reported, thereby emphasizing the importance of antifungal susceptibility testing. (13)

In summary, *C auris* exhibits uniform resistance to fluconazole, variable susceptibility to the other azole antifungals and a low acquired resistance to amphotericin B and the echinocandins. (25)

ANTIFUNGAL THERAPY

The first-line therapy is an echinocandin, pending the results of susceptibility testing, which should be carried out without delay. (27) Duration of antifungal therapy is like other infections caused by other Candida spp. In candidaemia, treatment should be continued for 14 days after resolution of symptoms attributable to candidaemia and also documented evidence of clearance of Candida from the bloodstream. (27) A novel drug, SCY-078, the first orally bioavailable 1, 3-β-D-glucan synthesis inhibitor, has demonstrated potent antifungal activity against various *Candida* spp including *C. auris.* (14)

INFECTION PREVENTION AND CONTROL

Similar to other *Candida* infections, *C. auris* infections appear to be hospital acquired, occurring several days to weeks into a patient's hospital stay. (12, 27) This suggests an exogenous rather than endogenous source of infection and a breach of infection control procedures. In cases of infections, environmental sampling has showed persistent presence of *C. auris* around bed space areas. (3) Implementation of strict infection control is therefore of paramount importance in the control of this infection. (11)

Cases and their contacts should be cohorted / isolated; and patient housed in a private room. Before de-isolating the patient, a series of three negative screens taken 24 hours apart is advocated. (27) To decrease the risk for transmission, health care personnel in acute care settings should use Standard and Contact Precautions. Personal protective clothing including cuffed long-sleeved disposable gowns, gloves and aprons should be worn by health care workers. (3) Decolonization of *C. auris* infected patients can be performed using chlorhexidine formulations depending on the site. Oral nystatin can also be prescribed if oropharyngeal colonization is present. (3) Environmental decontamination can be implemented using chlorine-based products and hydrogen peroxide vapour. (3)

When transferring colonized patients to other health care facilities, the receiving facilities need to be notified of the presence of this multidrug-resistant organism so as to ensure that appropriate precautions are adhered to. There should be thorough daily and, also on discharge of patient, terminal cleaning of rooms of patients infected with *C. auris* infections, using a disinfectant active against *Clostridium difficile* spores. (11, 20) Equipment used for patients should be cleaned and disinfected with hydrogen peroxide vapour. (3) Screening for *C. auris* in units having patients with ongoing infections or patients coming from other affected hospitals/units or patients at risk for candidiasis may be conducted. Suggested screening sites are: Nose, throat, and groin, urine/urethral swab, perineal or low vaginal swab, sputum/endotracheal secretions, wounds and other appropriate sites. All screen-positive patients should be isolated or cohorted. (27)

PROGNOSIS

Candida auris is an emerging healthcare-associated fungal pathogen associated with high mortality rate of 40-70%. (12) (1) Patients may have therapeutic failure with persistent candidaemia in spite of antifungal treatment which results in fatal outcomes. (6, 9, 20)

Recurrent *C. auris* candidaemia occurring 3 to 4 months after the initial episode of infection is another complication that may be encountered *C. auris.* (20)

Overall outcome is usually better when infection prevention measures are in place. (18)

LEVEL OF PREPAREDNESS IN NIGERIA AND FUTURE DIRECTIVE

Nosocomial outbreaks as well as recovery of laboratory confirmed isolates of *C. auris* have not been reported in Nigeria. More assertive infection control measures and steps should be put in place to prevent

the transmission of the organism in our health care settings. *Candida auris* infection should be suspected when the isolate is recovered from the critically ill patients in different Intensive Care units (ICU) in our tertiary hospitals. According to the recommendation of Centre for Disease control (CDC), all *Candida* isolates recovered from sterile sites should be identified to the species level so that initial empirical treatment can be administered on species -specific antifungal susceptibility patterns(28, 29). All healthcare facilities in Nigeria with high clinical suspicion of inpatients with *C. auris* should contact the local authority as well as the Federal Ministry of Health (FMoH) for notification.

Medical laboratories should emphasise the importance of accurate species identification for *Candida* to a species level. Many Medical Microbiology laboratories do not routinely speciate non-*Candida albicans* isolates or utilize yeast identification methods such as chromogenic agar, biochemical tests (API) or automated systems such as VITEK which do not speciate this pathogen or may misidentify *C. auris* as yeasts such as *Candida haemulonii, Candida sake*, and *Rhodotorula mucilaginosa*.(30) Clinical laboratories should be encouraged to forward *C. haemulonii* isolates and isolates not identified beyond *Candida* spp. by conventional methods to tertiary or public health laboratories in Nigeria for further characterization.

Antifungal resistance is an important concern in managing invasive Candida infections, Therefore, understanding drug susceptibility of these different species can help develop protocols for appropriate empirical treatment of these infections. We recommend that each hospital should put in place good antimicrobial stewardship programme and monitor the antifungal susceptibility pattern against this organism. In addition, each hospital should develop their guidelines and policies for the control and prevention of *C. auris* infection.

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CONCLUSION

There should be high level of clinical suspicions when non-albicans *Candida* are isolated in high risk patients admitted in intensive care units. Antifungal susceptibility testing should be initiated and performed routinely in all our tertiary hospitals and public medical microbiology laboratories. If there should be any report of positive cases, infected patients should be cared for in an isolated single room to prevent transmission of the pathogen.

Other aggressive infection control measures should be implemented in the hospitals. These include stringent hand hygiene procedures before and after touching the patients and items around the bed sides; cleaning of affected clinical areas with high strength chlorine-based agents and prompt treatment of patients with antifungal agents.

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