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Newly Emerging *Candida* Specie: Should Clinicians and Mycologist be Concerned?

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OFA and ASK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KM, MUI and AAY managed the analyses of the study. Authors OFA, NMB and SUN managed the literature searches. All authors read and approved the final manuscript.

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Mini-review Article

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ABSTRACT

The emergence of *C. auris* as a global nosocomial pathogen associated with multidrug resistance and high mortality rates has been recently discovered. This emerging pathogen appears to be far more able to induce systemic infection and mortality than other potential multi drug resistance (MDR) yeast pathogens even though it is found to have reduced virulence factors compared to *C. albicans*. There are issues with regard to the identification of *C. auris* using both phenotypic and molecular techniques; this has raised concerns about detecting the true scale of the problem. This mini- review elucidates on the literature available on *C. auris* and highlights the mechanism of pathogenesis and antifungal resistance, which will give further direction to extensive research in this field.

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1. INTRODUCTION

Reports show that an estimated 1.5 million people die annually from invasive fungal infections [1]. This is due to advance of life expectancy, the rise of immunosuppressive treatments, improved health care, higher survival of patients living with cancer or chronic disease and the use of catheters. These factors have all contributed to the emergence of opportunistic fungal pathogens over the last decades [2,3]. *Candida albicans* is recognized as the main causative pathogen of candidiasis [1]. However, with the rise of new species such as the globally emerging multidrug-resistant *Candida auris*, there might be a shift in focus. The first isolated multi-drug resistant *Candida auris* was in 2009 from the ear canal of a 70 year old female Japanese patient in Tokyo [4].

Treatment options of *C. auris* are limited mostly due to its ability to persistently colonize hospital environments, antifungal resistance, and misidentification. It has been associated with infections and outbreaks in healthcare settings in Europe, Asia, North America, South America, and Africa [5,6]. Recent reports have demonstrated that *C. auris* usually expresses fewer virulence factors than does *Candida albicans* [7]. However, *C. auris* possess the tendency to be transmitted within and between healthcare facilities which could possibly be promoted by its virulence and pathogenicity factors that allow it colonize the skin and persist in the environment [7].

Even though the complete genome of *C. auris* has been recently investigated, [8,9] the role of different genes in the pathogenicity and virulence of this emerging pathogen is not yet fully understood.

The main problem is that the *C. auris* genome sequence contains many uncharacterized and un-researched hypothetical proteins; it is therefore unclear whether these proteins are involved in species-specific characteristics that promote its aggressiveness as a pathogen [8] Four distinct clonal clades which was shown by whole genome sequencing emerged simultaneously on three continents, South America, Asia and Africa, and these four clades have been responsible for further spread around the world. Despite being a newly emerging pathogen, *C. auris* has been associated with large healthcare outbreaks around the world. The unique aspects of *C. auris* epidemiology is its ability to spread clonally from patient to patient as both a pathogen and a colonizer [5,10]. This mini-review will attempt to provide information regarding the pathogenesis and mechanism of antifungal resistance in *C. auris.*

2. PHENOTYPIC TRAITS AND ITS IMPORTANCE IN PATHOGENICITY

Candida. albicans is well-known to undergo phenotypic white-opaque switching and morphological yeast filament transition [11]. In a recent study by Bentz and co-workers [12], a phenotypic switching in *C. auris* when cultured onto CHROMagar Candida, was reported. *C. albicans* and *C. tropicalis* can be relatively reliably identified via a colony color change (*C. albicans*—green, *C. tropicalis*—navy blue) while other clinically relevant Candida species, including *C. auris*, showed a pale appearance. When the *C. auris* isolate was further cultured, it led to the description three colony types: white, pale and sectored (dark purple). However, there were no observed changes in the texture as all colonies displayed a smooth and glossy look [12].

Hyphae production by *C. auris* provides the fungus with the ability to invade epithelial cell layers by exerting mechanical force. This leads to the breaching and damaging of endothelial cells, which causes the lysis of macrophages and neutrophils following phagocytoses [13].

C. auris colonies may present pseudohyphae-like forms under high-salt stress [14] and, occasionally, in the biofilm community [15], although micromorphological studies suggest that it does not produce germ tubes, pseudohyphae or chlamydospores [16,17,18,19]. Pseudohyphae-like features show rudimentary growth, with an elongated shape and incomplete cell division [15,14]. Its inability to produce hyphae could be linked to the absence of two genes, candidalysin (*ECE1*) and hyphal cell wall protein (*HWP1*). Transcriptions of these genes are strongly associated with hyphal formation and are highly expressed in *C. albicans* [19].

Using the *Galleria mellonella* model of infection of *C. auris*, isolates did not undergo significant filamentation at 18 h or at any time post infection.

This confirmed the failure of *C. auris* to form chlamydospores after growth on cornmeal agar when incubated for 3 days at 30°C and its inability to germinate when cultured with fetal bovine serum (FBS) [20].

Certain isolates of *C. auris* grow in clumps (i.e., budding occurs, but daughter cells are not released), these isolates are called “aggregate” strains. This aggregate strains result in large aggregates of organisms that cannot be easily disrupted *in vitro* [20]. There are suggestions that aggregation might be a mode of immune evasion and persistence in tissues. This is because yeast cell aggregates were observed in the kidneys of mice infected with *C. auris* in a study conducted [21]. However, this warrants further investigations. It is obvious that phenotypic traits could be of great importance in the pathogenicity and virulence of *C. auris.*

3. ABILITY TO TOLERATE STRESS

Survival and growth at physiologic temperature are prerequisites for microbial invasion and pathogenicity. *C. auris* exhibits thermotolerance, growing optimally at 37°C and maintaining viability up to 42°C. In addition, this pathogen is salt tolerant, and cells aggregate into large, difficult-to-disperse clusters, which may promote persistence in the hospital environment [4,19]. The ability of *C. auris* isolates to grow at 37°C and 40°C appears to be similar to that of *C. albicans*, and certain isolates also grow at 42°C [21]. *C. auris* can also grow at high temperature (40°C) and salinity (10% wt/vol) when cultured in Sabouraud (SAB) or yeast nitrogen base (YNB) broth with dulcitol or mannitol as the carbon source [22].

4. PRODUCTION OF HYDROLYTIC ENZYMES

Extracellular hydrolytic enzymes produced by Candida species is an important virulence trait contributing to its pathogenicity. The ability to produce lytic enzymes has been demonstrated in *C. auris* isolates, and the production of these enzymes is strain dependent [23, 24]. The most common virulence associated enzymes are the proteinase. hemolysins, lipases and phos-pholipases, which play crucial roles in the virulence of the species [23,24]. These enzymes are considered to play a role in the degradation of host tissue to provide nutrients for pathogen propagation. Protienases has in recent times been associated with cell wall maintenance, the formation of polymicrobial biofilms, adhesin to external protective barriers of the host, deregulation of the complement system, inactivation of host antimicrobial peptides, evasion of the immune responses and the induction of inflammatory mediator release from host cells [23,24,25].

Findings suggest that *C. auris* isolates are not only well able to adapt to temperature stress but can maintain their ability to secrete hydrolytic enzymes even at higher temperatures. This was demonstrated by Wang et al. [17] whose findings showed that the level of aspartyl proteinase (Saps) secreted by *C. auris* isolates at 42°C was higher than that exhibited by *C. albicans* at the same temperature [17]. The largest group of enzymes (42%) found in the *C. auris* (strain 6684) genome, are the hydrolases. This is followed by transferases (25%) and oxidoreductases (19%) [8]. Similar numbers of lipases have also been revealed by genome analyses [23,24].

The secretion of hemolysin by *C. auris* promotes survival in mammalian host, conferring a high capacity for iron acquisition, growth, and invasiveness leading to widespread infection [25, 26,27]. Hemolysin activity enables *C. auris* assimilate iron from the hemoglobin-heme group [28]. *C. albicans, C. dubliniensis, C. glabrata* and *C. tropicalis* also display hemolysin activity [28,29,30,31]. Hemolysin production can be seen as an important virulence factor because it is higher in strains isolated from hospital infections compared to those from environmental sources [1]. However, further investigation is warranted to reveal to what extend these enzymes are involved in *C. auris* virulence and pathogenicity.

5. COLONIZATION OF HUMAN HOST AND THE ENVIRONMENT

C. auris can extensively contaminate health care environment. It possess the ability to adhere to and persist on abiotic surfaces, including dry and moist surfaces, bedding material, floors, sinks and beds, as well as human skin, ears, and nasal cavities [32,33,34,22]. This characteristic enables it to be colonize and spread through hospital environments. *C. auris* can remain viable for at least 14 days on health care surfaces [21], there has been reports of Nosocomial *C. auris* outbreaks in hospitals globally, some of them persisting up to 16 months [34]. A case of *C. auris* sternal osteomyelitis in a patient who was colonized by *C. auris* 3 years prior to clinical disease manifestation has been described [35].

Although, *C. auris* is able to persist on health care surfaces, Catheter-associated candidiasis caused by *C. auris* is reduced relative to C. albicans because the fungus shows a weak ability to adhere to catheter surfaces made of silicone elastomer [26].

There are several reports on the suboptimal efficacy of commonly used hospital environment disinfectants against *C. auris.* Quaternary ammonium-based disinfectants seem to be significantly less effective against *C. auris*, but also against C. albicans and C. glabrata [37,38]. CDC recommends EPA-registered hospital-grade disinfectants effective against Clostridium difficile spores (primarily chlorine-based products) be used to combat this infection [36,37,38]. Strict infection control guidelines should be instituted to establish effective infection prevention and transmission of *C. auris* via contaminated surfaces.

6. BIOFILM PRODUCTION LEADING TO ANTIFUNGAL RESISTANCE

C. auris is able to form biofilms (architecturally complex microbial community encased in a matrix of exopolymeric material). Biofilm production is crucial for the development of broad spectrum of infections in the host. It is also useful for defending pathogens from invasion and in the development of antifungal resistance [39].

Upregulation of seven highly conserved genes (*PLB3, IFF4, PGA52, PGA26, CSA1, HYR346,* and *PGA7*) is responsible for biofilm production across isolates representative of *C. auris*, *C. albicans, C. haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii* [40]. The *C. auris* biofilms mostly consists of budding yeasts and occasionally pseudohyphae embedded in a limited amount of extracellular matrix. Biofilm formation contributes not only to *C. auris* virulence but also to resistance in hospital environment. This biofilms display lower susceptibility against antifungals, including caspofungin, micafungin and amphotericin B [41].

C. albicans biofilms consists of basal yeast cell polylayer and an upper region of hyphae encapsulated in extracellular matrix, whereas *C. glabrata* forms a thin biofilm with yeast cells only, lacking extracellular matrix [41].

Candida biofilms are able to show intrinsic resistance against antifungals due to several mechanisms: (1) the high cell density within the biofilm; (2) decreased growth rate and nutrient limitation; (3) sequestration of drugs by the extracellular matrix (ECM); (4) the high expression of resistance genes, especially those encoding efflux pumps; and (5) the presence of 'persister' cells [41,42].

7. CONCLUSION

The recent emergence of *C. auris* as a global nosocomial pathogen associated with multidrug resistance and high mortality rates is a cause for concern. Although several studies show that *C. auris* has reduced virulence compared to the more popular *C. albicans,* this emerging pathogen ability to persist in the environment and colonize surfaces makes it more able to induce systemic infection and mortality than other potential MDR yeast pathogens, such as *C. glabrata* and *C. haemulonii* [43].

This is likely due to the tolerance of *C. auris* strains to osmotic and high-temperature stress as well as to its ability to produce several lytic enzymes and biofilm [21, 22].

There is however still some questions to be answered such as the origin of this unprecedented emergence. Genomic analyses revealed *C. auris* possesses many genes associated with virulence and reduced antifungal susceptibility, nonetheless, many genes are still uncharacterized and further investigation is required to understand the molecular mechanism responsible for the high pathogenicity and antifungal resistance of this pathogen [8,19,3].

Adhesins and other molecules responsible for the capability of *C. auris* to persistently colonize abiotic and biotic surfaces should also be given due attention as its characterization will enable understanding on the ability of *C. auris* to survive and persist under different environmental conditions [21,22].

In conclusion, there are many unanswered questions about the emergence of *C. auris* and its seemingly unique traits such as the ability to evade the innate immune system and persistently colonize the skin of human host [44]. With several researches ongoing, we are hopeful that in no distant time, we would fully be able to understand the various mechanisms for the emergence of *C. auris* as a nosocomial pathogen.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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