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Article

Descriptive View on Candida Auris Occurrence in a Tertiary Health Institution in Riyadh, Saudi Arabia

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Abstract: Background: *Candida auris* is an emerging multidrug-resistant fungal pathogen that represents a serious threat to healthcare settings currently. Objective: Its objective was to determine the prevalence of *C. auris* in the hospital since its initial detection in late 2019. Methods: Using an adapted risk assessment tool, we reviewed the charts? and medical files of all suspected? and confirmed cases of *C. auris* cases reported at King Khalid University Hospital, Riyadh between November, 2019 and December 2022. Anonymized data were retrieved in a pre-established datasheet and analysed to determine the epidemiological characteristics of *C. auris* infection in our facility. We established our initial prevalence by age, gender, risk factors, and according to sampling source. Results: Of the 53 confirmed cases positive for *C. auris* during the study period, 33 (62%) were males. Their ages ranged between 15 and 98; most positive cases occurred in 50 and above. Only one of the confirmed cases was hospital-acquired. All patients had at least one risk factor, and Urine samples yielded the greatest number of positive cases while admission to healthcare facilities constituted the highest risk in our study. Conclusion: Establishing a local prevalence could serve as our baseline/benchmark to compare with regional and international bench marks.

Keywords: *Candida auris*; *C. auris*; candida; candidemia; multi drug resistant organism; MDRO; emerging pathogens; resistant pathogens

1. Introduction

This study investigated the incidence of *Candida auris* in a tertiary care teaching hospital located in Riyadh, Saudi Arabia. The *C. auris*, first emerged in 2009,[1] and has continued to cause hospital-acquired infections in individuals with compromised immune systems and has also been associated with persistent candidemia and high mortality rates globally.

Candida auris was first identified in 2009 when it was found in the outer ear of a patient in Japan [2]. Since then, clinical cases of *C. auris* infections have been reported in in other countries including South Korea [3], India [4], Pakistan [5], South Africa [6,7], Canada[8] with a phenomenal surge between 2018 and 2021 in the United States [9].The first Saudi case was reported in 2018 [10] and later followed by several reports from other parts of the country [11,12].

This fungal specie is rapidly spreading worldwide, with several outbreaks [13] reported from five continents in recent years. [4] Between the years 2019 and 2020, *C. auris* has been reported in over

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40 countries across the world. The Asian continent has the highest number (14) of countries where *C. auris* is reported, followed by Europe (13), and then trailed far behind by South America (4), Africa (4), North America (3), and Oceania (1) [14].

The surge in the incidence rates of candidemia has been an immense burden on public health, particularly among patients in intensive care units. [5,7]. The mortality rate is higher among infected patients compared with those who were colonized. [15] *C. auris* is an opportunistic pathogen that can cause candidemia [16] with risk factors including immunocompromised patients, patients with organ transplants, diabetic patients, or patients on recent antifungal use, catheter use, and prolonged ICU stay. [9] Other risk factors include chronic kidney diseases, recent vascular surgery, or surgery within the previous three months.[17,18]

C. auris started attracting considerable global attention due to its growing reports, transmission through health professionals, high rate of treatment failure, and multidrug resistance.[19] *C. auris* is increasingly becoming a threat to human health because of its intrinsic resistance to 1 or more classes of antifungal drugs [14,20] However, other studies have noted that *C. auris* is less resistant to 5-fluorocytosine and caspofungin.[21]

Whole genome sequencing has identified geographically distinct *C. auris* genotypes thus suggesting the region-specific resistance and transmission patterns. [22] Therefore, the multidrug resistance of *C. auris* are geographically expressed as thus: Clade 1: South Asian; Clade II: East Asian; Clade III: African; Clade IV: South American and recently, Clade V: Iranian.[23] Although the clades are attributed to specific geographical locations, a mixed isolates may be found in a single location[22,24] Accordingly, a study has documented trans-border importation of *C. auris* by patients with recent exposure to healthcare in another country where *C. auris* has been reported. [8]

It is difficult to identify *C. auris* using the traditional fungal identification methods, [25] and can lead to wrongful identification. [9,25] Owing to their close genetic relatedness, as a haploid fungal specie, *C. auris* is often reported as *C. haemulonii* [26,27] while using conventional identification systems like APIC20C, Vitek2YST and BD Phoenix, [28] and, as *C. parapsilosis* using the RapiID[29] thus, necessitating additional testing methods with higher specificity to elicit species identification.[30,31] A mis-identification of *C.* auris can potentially result in incorrect treatment or delay of proper treatment with increasing chances of fatalities. [32]

Similarly, there are currently no established *C. auris*-specific susceptibility breakpoints, but clinicians often rely on their expert opinion and previously established breakpoints for other related *Candida* species. Currently, there is no evidence of relationship between microbiologic breakpoints and clinical outcomes. [33]

Furthermore, some of the epidemiological distinctiveness of *C. auris* include its swift transmission,[34] and its resistance to conventional disinfectants. [35,36]. Unfortunately, *Candida auris* is considered among the most virulent environmental pathogens that are associated with hospital transmission.[13] It can survive on surfaces for a prolonged period.[1]Also, a recent isolation of *C. auris* from a natural aquatic habitat in India indicates that this fungus may also exist without a human host.[37]

As *C. auris* is fast spreading within healthcare settings, it has become imperative to monitor its virulence and devise appropriate treatment approaches [9] in view of the several hospital-associated transmissions reported globally.[38–40] Therefore, an early detection and implementation of infection control practices can potentially reduce the risks. [18,35] Consequently, understanding its epidemiology can significantly help in planning specific infection control measures for healthcare settings.[41,42] Accordingly, this study aims to provide a descriptive overview on the occurrence of *C. auris* in the hospital since its initial detection in late 2019.

2. Methodology

This is a retrospective study of patients had been reported with *C. auris* at a tertiary healthcare institution during the period from Nov 2020 to the end of 2022. It was during this period that the hospital started recording additional *C. auris* cases (after our first case in November 2019), and

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specific infection prevention and control measures were adapted and implemented to minimize hospital associated transmissions within the hospital.

2.1. Data Collection

Although no patient identifiable data is used for the reporting, an Institutional Review Board Approval No. No. 22/0701/IRB was obtained before proceeding with the research. The ethical approval required us to abide by the rules and regulations of the Kingdom of Saudi Arabia and the research policies and procedures of the KSU IRB related to data privacy.

Accordingly, all data are mined from the hospital's electronic health information system (*eSIHI*) after properly anonymizing, i.e., after removing the patient's medical record number, national identification number, nationality, names and any other patient identifiers. Data on patients' demographic information, baseline features, comorbidity, laboratory results, and clinical outcome were then compiled in an Excel worksheet and analysed after reviewing the electronic patient records.

2.2. Specimen Sampling

All *C. auris* strains identified in the lab throughout the research period from both clinical and surveillance screening samples were included. For the purpose of inclusion, all active surveillance samples, all contact tracing samples and all clinical samples are considered. Surveillance samples include those taken when it is determined that the risk factors for colonization or infection exists, or if an inpatient is included as a contact of a positive case (as part of contact tracing). See **Table 1** for the list of risk factors included. Active surveillance samples taken include nasal, axilla, groin, wounds, indwelling device sites etc. Additionally, based on clinical assessment other sites were potentially included like the anus, chronic wounds, blood, urine, wound, tissue, drains etc. For the purpose of the study, only the first positive isolate per patient was included.

Table 1. Risk Factors for C. auris.

Bundle Element/Risk Factor	Score
History of Admission from other hospital,	3
Has any of these: Septicaemia + CKD, DM, or chronic lung disease	1
Previous history of MDRO infection or colonization	1
History of admission in hospital outside the KSA (within the past 12 months)	1
Presence of wounds or indwelling devices,	1
Admission to high risk units (ICU, HDU, Oncology etc)	1
Contact of MDRO / ASC	1
Previous surgery < 3 months	1

HDU: High dependency unit; ICU: intensive care unit; ASC: active surveillance culture; KSA: Kingdom of Saudi Arabia.

2.3. Testing and Identification

Surveillance swabs were cultured on Sabouraud dextrose agar with chloramphenicol and incubated at 37 C° for 48 hours. Any growth of yeast from surveillance samples underwent identification. Additionally, significant growth of yeast from clinical samples (e.g., blood, urine, wound etc.) was identified. Yeast identification from surveillance and clinical samples was done using the matrix assisted laser desorption ionization time of flight mass spectrometry (biomerieux, Marcy-l'Étoile, France).

2.4. Determining Hospital Associated Transmission

And, for the purpose of determining if a *C. auris* isolate is to be considered hospital or community acquired, the study adopted the epidemiological definition of hospital acquired

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infections coined by the National Health Safety Network of the USA.[43] The Network considers as hospital acquired, any infection that is determined not to be "present on admission (POA)".

An infection is considered as POA if an element of the specific infection criterion manifests during the POA window period i.e., 2 days prior to an inpatient admission, on admission date, and the calendar day after admission. In other words, if an element (sign, or symptom) occur after the second calendar date, it is considered as hospital acquired infection.

And therefore, if a sample is taken after the second calendar date of admission and the patient did not exhibit any symptom before the third calendar date, the isolate is considered as being hospital acquired.

2.5. Statistical Analysis

Statistical analysis was done by SPSS version 28 (IBM Co., Armonk, NY, USA). The inclusion criteria for the multivariable analysis is based an epidemiological criterion derived from the risk factors identified and selected, the patient's demographic information, and the outcome of the disease. The study then expresses categorical data in a form of frequency and percentage (%), with statistical significance is noted where a two-tailed P value is < 0.05.

3. Results

A total of 53 patients (33 males and 20 females) with *C. auris* were included in this study. Urine specimens were the most frequently obtained sample in 30.2% of patients followed by axilla from 11.3% then thigh and anal specimens, each from 9.4%. Samples labeled as buttocks and hip are lumped with that of the thigh, the proportion of sample source for the thigh would be 18.8% (n/10) second highest to the urine samples.

3.1. Prevalence: Age

The median age of screened patients was 64 years (inter-quartile range (IQR) 15 – 98). A further analysis of *C. auris* incidence by age (**Table 2**) showed a drastic increase in the incidence of *C. auris* among patients aged 51 years and above with a stair-case raise with every new decade of age above 51.

Table 2. Patients' characteristics (n=53).

	N	%
Age (years)		
≤20	2	3.8
21-30	4	7.5
31-40	3	5.7
41-50	2	3.8
51-60	13	24.5
61-70	14	26.4
≥71	15	28.3
Gender		
Male	33	62.3
Female	20	37.7
Specimen		
Urine	16	30.2
Axilla	6	11.3
Thigh	5	9.4
Anus	5	9.4
Arm	4	7.5
Swab	3	5.7
Penis	3	5.7

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Hip	3	5.7
Nose	2	3.8
Buttock	2	3.8
Leg	2	3.8
Neck	2	3.8
Nasal	2	3.8
Tissue	1	1.9
Wound	1	1.9
Nail	1	1.9
Rectal	1	1.9
Blood	1	1.9
Foot	1	1.9

3.2. Prevalence: Patient Characteristics

Additionally, most patients (83%) had comorbidities, while half (50.9%) of them having been previously admitted to other hospitals. Other risk factors include admission to high-risk units (35.8%), wounds, and indwelling devices respectively in 34% and 32.1% as summarized in **Table 3.**

Table 3. Patients' Characteristics.

	N	%	95% CI of rate
Comorbidities	44	83	60.3 to 111.5
Admission to other hospital	27	50.9	33.6 to 74.1
High Risk Areas	19	35.8	21.6 to 56
Wounds	18	34.0	20.1 to 53.7
Devices	17	32.1	18.7 to 51.4
Antimicrobials	12	22.6	11.7 to 39.6
ASC	11	20.8	10.4 to 37.1
Surgeries	7	13.2	5.3 to 27.2
MDRO	1	1.9	0.0 to 10.5
Outside KSA	0	0.0	---
Contact of MDRO	0	0.0	---

CI: Confidence interval.

3.3. Prevalence: Hospital versus Community-Acquired C. auris

Out of the 53 isolates identified in the study, only one meets the epidemiological definition of hospital-acquired *C. auris* infection/colonization. In other words, as per the NHSN surveillance definition of hospital-acquired infections alluded to in the methodology section, all but one was identified as being POA during active surveillance screening.[43] One case, considered as hospital acquired, was on admission for longer than one week when his condition worsened and a clinical sample tested positive.

3.4. Prevalence: Infection versus Colonization

Out of the 53 isolates included in this study, seven (7) cases as their clinical specimens were taken when the patient's condition worsened and required ICU admission. Four (4), out of the seven that required ICU admissions, developed *C. auris* candidemia. Therefore, out of the total of 53 cases, 4 are considered as *C. auris* infections and the remaining 49 are considered as colonization.

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3.5. Prevalence: Clinical versus Surveillance samples

Our sample size includes 7 clinical samples and 46 active surveillance samples. This explains the vigor with which we have endeavored to identify all possible patients that are a risk of *C. auris* infection/colonization for the purpose of proactively identifying and isolating all positive cases. The proportions of clinical versus surveillance samples could, respectively, identify already sick (potentially infected) patients who are not necessarily sick, but maybe colonized and picked during the surveillance sampling. This could be useful in distinguishing our prevalence from other comparable hospitals. For instance, in a recent Saudi Arabian study[11] where 27 patients with invasive candidemia were studied for their risk factors and mortality, their prevalence cannot be compared with ours as we had a greater number of colonized patients and only one infected patient.

4. Discussion

Our study's strength, however, comes from the fact that it is the first in Saudi Arabia to give verifiable proof of the prevalence of this infamous yeast in hospital settings. It seems evident our findings echo conclusions from several other studies that *C. auris* is already prevalent across the globe, although in different proportions. For instance, a systematic review by [44] has shown that, from January 2019 to January 2021, several countries, including those in the Middle East have reported a significant number of *C. auris.* From data collected from nine studies, they reported a number of cases from several countries; Kuwait: 71[45], Oman: 29 (from two separate studies) [46] and [47] Saudi Arabia: 35, Spain: 47 [48], Mexico: 12 [49] Kenya [50], and the USA: 47 (from two studies) [51] and [52] The totals shown here included both *C. auris* candidemia and colonisations.

Most of the patients (clinical and active surveillance) from which C. auris confirmed samples were retrieved were males (33;62%) (Table 2). This is consistent with the findings of a retrospective analysis of the clinical characteristics of *C. auris* infection worldwide from 2009 to 2020.[42] and another study where 62% of the patients were male.[53]

The first three cases of *C. auris* were reported in Saudi Arabia in the year 2018 [54] and subsequently reported in other parts of the Kingdom [55–57] The United Arab Emirates, too, reported its first case of *C. auris* candidemia in the same year as with the Kingdom of Saudi Arabia.[58] Six other Middle Eastern countries also followed suit. All of those patients, all adults, were also initially misdiagnosed as *c. haemulonii* were. [28]

It is noteworthy that the first case of *C. auris* was reported in our health facility in late November of 2019, and our prevention and control measures were overshadowed by the declaration of COVID-19 as a global pandemic in March, 2020.[59] A number of factors have complicated the treatment of COVID-19 co-infecting with *C. auris* during the COVID-19 pandemic. Such factors include the multi-drug resistant nature of *C. auris,* their shared risk factors including co-morbidities, immunosuppressive states, and mechanical ventilator dependent states. [60] Therefore superimposed *C. auris* infection in a COVID-19 patient could exacerbate the severity of secondary comorbidities, including severe lung injury, acute respiratory distress syndrome (ARDS) and heighten mortality rates among critically ill patients.[61,62] Another similarity between the two pathogens is that they are both found on patient care environmental surfaces e.g., floors and air ducts making transmission among ventilated patients easy.[63]

During the first 6 months of the study period (November 2019 to April 2021), 4 (active infections and/or active surveillance) cases were reported. However, through the remaining three-quarters of the year 2021, there were between 1-3 cases reported monthly. This could be associated with the optimization of the *C. auris* identification and control measures during the period. March 2022 marked the peak of the graph with 9 cases being reported. This period marked a massive active surveillance screening of many patients that had unprotected contact with an index *C. auris*-positive patient. There was then a steady stair-case increase in cases? from June to September 2022 until it final declined to zero in December 2022. **See Figure 1**

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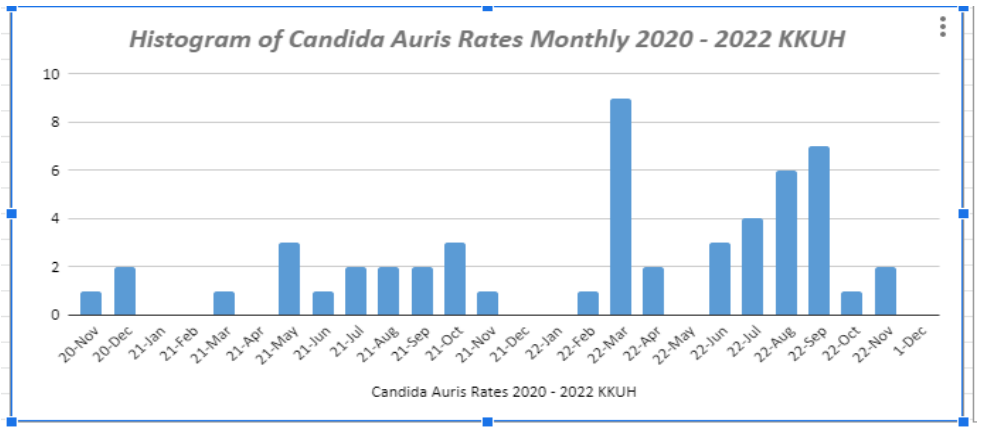

Figure 1. Histogram of *C. auris* rates 2020-2022.

As shown in **Table 2,** the incidence of *C. auris* according to age which has shown that there was a sharp rise in the incidence from the age of 51 and above. There was also a staircase-fashioned increase by each decade from the attainment of the golden jubilee and beyond. This is consistent with the findings in other reports where nearly half of the cases were around the age of 70 years.[64,65]. A similar Omani study has shown that out of 108 patients, 40 (37%) were >65 years of age.[66] However, a South African study that compared, among others, the age distribution of patients with candidemia caused by *C. auris* with other candida species, has shown the incidence is highest among neonates, followed by those in the 40-70 years age bracket, but lowest in the 10 – 20 years age range.[67] However, as opposed to our findings, there was a steady decline in the rates with the advance in each decade of age from 50 years. The bottom line would seem to be that extremes of age are a significant risk factor for *C. auris*.

Among the samples taken with positive results for *C. auris,* our study showed that urine samples yielded the highest number of cases (30.2%), followed by samples taken from the thigh, buttock, and hip, clumped together (18.8%), axilla (11.3%) and others taking the remaining balance. There was only one case of candidemia reported. Most samples (n=?) were taken during enhanced active surveillance rather than as diagnostic samples in suspected clinical infections (**Table 2).**

Although the first case of *C. auris* was found in Japan from the ear, thus the name, *auris*.[2] it has since been found in different parts of the body. In a study of 108 clinical samples with *C. auris* isolates, the most common sample was blood (38.9%), urine (36.3%), respiratory (8%), central line tip (8%), wound (6.2%), and other samples (2.6%).[66] It has also been found in bronchoalveolar lavage, [68] diabetic foot tissue culture, etc., [69] that is consistent with findings in several other studies of clinical samples. [70] It is noteworthy that their study involved a majority of clinical samples taken from sick patients while our study includes a majority of surveillance samples with quite a few clinical samples. Although they are distinctively different classes of microbes, *C. auris* cases are similar to MDROs in their risk factors, environmental source, and mode of transmission and, patients infected with *C. auris* are often co-infected with other MDROs. [8,71]

As shown in **Table 3**, a review of the patient's characteristics revealed that all of the reported cases (100%) had at least one risk factor, similar to findings in other studies where 98.1% had at least a risk factor.[66] Also, 83% of our studied patients had some co-morbidities that include chronic kidney diseases, septicemia, diabetes mellitus, or chronic lung disease. As reported in the results, 50.9% had been admitted to other hospitals, while admission to a high-risk unit followed with 35.8%. Patients with wounds constituted 34% and those with devices were 32.1%. Devices implicated include urinary catheters, central venous catheters, and mechanical ventilator. Our findings seem to reiterate the findings of other studies. In an Omani study, 68.5% had comorbidities[66] while a New York study showed that extensive healthcare exposure and underlying comorbidities constituted significant risk factors in the reported cases.[65]

It is noteworthy that an alternative approach: multiparametric approach may have been successfully used in some research, e.g., to identify high-risk prostate cancer (with a Gleason score of

at least 7) with better sensitivity and specificity than that provided by PSA screening alone.[72] However, our approach is to identify and isolate potentially infected or colonized patients based on epidemiological criteria for the purpose of early recognition and isolation, and not on clinical criteria for treatment purposes.

However, this study is not without limitations. Being the first study of its type within the Kingdom, and the lack of regional benchmark to compare our rates with, it is difficult to posit our prevalence rates in relative terms. Also, the use of risk factors for active surveillance screening might not be so specific as compared, for example, with a multiparametric approach. We might have overlooked a few situations.

The inherent risk of misdiagnosis or wrong identification could result in missing out on some potential cases of *C. auris* colonisations/infections. Although *c. auris* are properly identified, our hospital laboratory relied on the susceptibility of other candida species, or rely on expert opinion in deciding on appropriate antifungal treatment. This explains why we did not include the susceptibility results in our study.

C. auris is globally endemic and continues to spread within healthcare settings. Following our index case in November 2019, our enhanced active surveillance suggests that C. *auris* may be under-reported and its endemicity in the Kingdom more than what meets the eye. Enhanced active surveillance for *C. auris* and infection control measures could avert future nosocomial? outbreaks.

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Informed Consent Statement: Not applicable.

Data Availability Statement: Raw study data are not readily available online, but can be made available on request, following local regulations and policies.

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Conflicts of Interest: The authors declare no conflict of interest.

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