

Original Article

Clinical and laboratory features of patients with *Candida auris* cultures, compared to other *Candida*, at a South African Hospital

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Abstract

Introduction: Multidrug resistant *Candida auris* is an emerging threat worldwide. It has been identified in Africa, however, there is minimal data available comparing *C. auris* to other *Candida* species in Africa.

Methodology: Retrospective, case control study at a tertiary South African Hospital. Clinical and laboratory features of patients with positive *C. auris* clinical cultures from 1 January 2015 to 31 August 2018 were compared to patients who cultured *C. albicans* and *C. glabrata*.

Results: Forty-five clinical cases with *C. auris* cultures were identified. The median age was 32 years (IQR = 26-46). The median duration of hospital stay was 64 days (IQR = 39-88) and median time from admission to diagnosis 35 days (IQR = 21-53). Indwelling devices and previous antibiotic exposure were found to be significant risk factors. All *C. auris* isolates were susceptible to amphotericin B and micafungin. Patients treated with amphotericin B alone, had a higher mortality (73.33%, n = 11/15) than patients treated with an echinocandin (54.55%, n = 6/11), however this was not statistically significant. All *C. auris* isolates were healthcare associated with 80% (n = 36/45) acquired in ICU. The 30-day all-cause in-patient mortality was 42% (n = 19/45) for *C. auris*, 36% (n = 16/45) for *C. albicans* and 53% (n = 24/45) for *C. glabrata*.

Conclusions: *C. auris* is an emerging multi drug resistant threat in South Africa. Improved access to echinocandins and improvement of infection prevention and control strategies are imperative to prevent further morbidity and mortality due to this pathogen.

Key words: *Candida auris*; candidemia; drug resistant *Candida*.

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Introduction

Candida species are commensals of the skin and mucosal surfaces in healthy individuals. However, in immunocompromised patients, these fungi can cause invasive disease [1,2]. *Candida* species are a common cause of health care associated bloodstream infections [3,4]. In the past, *Candida albicans* was the predominant cause of infection, however, there has been a recent shift to non-*albicans* *Candida* species (NAC) causing disease [5,6]. *Candida auris* is an emerging species causing healthcare associated infections (HAI). First identified in 2009, from the external ear canal of a patient in Japan [7], it has since been identified in several countries globally, including South Africa [8-18].

Previously, the commonest *Candida* species, causing disease in South Africa, was *C. albicans* followed by *C. glabrata* [19-21]. However, 2016 National institute of communicable diseases (NICD)

surveillance, found that *C. parapsilosis*, was the commonest followed by *C. albicans* and *C. auris* ranked fourth [22]. Eleven percent of candidemia in South Africa was due to *C. auris* in 2016-2017; 94.2% of cases were in Gauteng province [23,24].

Length of hospitalisation prior to infection differs between species. The average number of days between hospitalization and *C. auris* infection was 24 days [14] and 27.5 days [15], in 2 studies, and 3.5 [25] days for *C. glabrata*. In intensive care unit (ICU) patients, the median length of stay prior to diagnosis was 25 days for *C. auris*, 14 days for *C. albicans* and 16.5 days for *C. glabrata* [12].

Detection of Beta-D-glucan (BDG) is found to be a useful adjunct for the diagnosis of deep-seated *Candida* infections due to *C. albicans* and *C. glabrata*. A South African study showed 71% sensitivity of BDG in *C. auris* candidemia [26].

Known risk factors for *C. auris* are urinary catheters, central venous catheters (CVC), underlying malignancy, chronic kidney disease, neutropenia, total parenteral nutrition (TPN), increased length of stay, mechanical ventilation, immunosuppressive states and prior broad spectrum antibiotic use [10-12,14,15,23,27]. Mortality ranges from 28-50% in published studies [10,12,14,15].

There are currently no established clinical breakpoints for *C. auris*, but the CDC has provided tentative breakpoints [18]. *C. auris* is the first *Candida* species to be classified as multidrug resistant. Studies from multiple countries have demonstrated resistance to fluconazole [9-12,14,15,28]. The CDC, Public Health England and South African guidelines recommend echinocandins as first line treatment. However, for eye, urinary tract, central nervous system infections and in infants under two months old, amphotericin B is recommended [18,29,30]. The South African public health sector has minimal access to echinocandins and negligible access to liposomal amphotericin B.

Aim of the study

Little information is available on the clinical aspects of *C. auris* infection and colonisation compared to other *Candida* species where virulence and antifungal resistance differs. *C. auris* has been found to be both equally virulent as *C. albicans* [31] and demonstrates high minimum inhibitory concentrations (MICs) to azoles, similar to *C. glabrata* [28]. The aim of this study was to determine whether clinical features, risk factors and outcomes of patients who cultured *C. auris* differed from those who cultured *C. albicans* and *C. glabrata*.

Methodology

Study population and study design

This retrospective, case control study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary public hospital in the Gauteng province of South Africa. A deduplicated list of *C. auris* isolates, during the period 1 January 2015 to 31 August 2018, was obtained from the National Health Laboratory Service (NHLS). A case of *C. auris* was defined as a positive culture, from any site, during the study period. The first positive specimen was included, and duplicates (cultured within the same admission) were counted as a single case. These cases were matched against patients with *C. glabrata* and *C. albicans* cultures. Cases were matched based on ward, age and site of culture. Patients with the closest age (within a 10-year range) were included.

Microbiological methods

Routine culture medium (5% sheep blood agar, chocolate agar and sabouraud dextrose agar) was used to culture *C. auris*. The Vitek 2® (bioMérieux, Marcy-l'Étoile, France) system was used for identification and susceptibility testing of yeasts. The CDC tentative breakpoints were used to interpret susceptibility results for *C. auris* and the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing guidelines were used for *C. albicans* and *C. glabrata* [18,32]. The Fungitell® assay (Associates of Cape Cod, Massachusetts, United States of America) was used for BDG testing and interpreted according to the manufacturer's recommendations. Microscopy of samples using standard microbiological methods were used for bacterial culture. The samples were plated out onto solid agar (including 5% blood, chocolate and MacConkey agar where appropriate). Additional media were dependent on the sample type. Identification of the bacteria was performed using Vitek® mass spectrometry matrix assisted laser desorption ionization- time of flight mass spectrometry (bioMérieux, Marcy-l'Étoile, France) or Vitek® 2 (bioMérieux, Marcy-l'Étoile, France) automated microbial identification and antibiotic susceptibility testing.

Data collection

Inpatient files were retrieved from archives. Information on demographics, clinical features, laboratory investigations within 24 hours of collection of the positive culture, risk factors, treatment and outcomes were entered into an anonymized Microsoft Excel spreadsheet.

Statistical analysis

Standard analyses were performed for the data. Microsoft Excel was used for basic analysis. Categorical variables were reported as frequencies and percentages and continuous variables were reported as median and interquartile range (IQR). Statistica™ (version 14) software was then used for further analysis. Continuous variables were analysed using the Mann-Whitney U Test and categorical variables were analysed using the Chi-Square Test. Confidence interval of 95% were used and *p* values < 0.05 were considered statistically significant.

Study definitions

- Healthcare associated infection: a positive *Candida* culture, more than 48 hours after admission,

Table 1. Patient demographics.

	<i>C. auris</i>	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. auris</i> vs. <i>C. albicans</i>	<i>C. auris</i> vs. <i>C. glabrata</i>
Number	45	45	45		
Age (Years), median (IQR)	32 (26-46)	38 (28-58)	38 (31-51)		
Gender, Males, n (%)	32 (71.1%)	26 (57.8%)	27 (60%)	<i>p</i> = 0.186	<i>p</i> = 0.267
Total length of hospital stay (days), median (IQR)	64 (39-88)	27 (14-37)	21 (12-44)	<i>p</i> < 0.001*	<i>p</i> < 0.001*

* statistical significance.

associated with clinical or laboratory features of infection.

- ICU acquired candidiasis: Culture of *Candida* species obtained 48 hours after ICU admission or within 48 hours of discharge from ICU.
- Antifungal exposure: empiric or prophylactic therapy with an antifungal agent up to 30 days prior to the diagnosis of candidiasis.
- Outcome: determined 30 days after the diagnosis of candidiasis.
- Thirty day all cause in-patient mortality: number of patients who died whilst still in-patients, within 30 days of onset of candidiasis, regardless of cause of death.
- Temperature spikes: an intermittent sharp rise in body temperature, with resolution to baseline. These intermittent increases in temperature lasted between 24 and 48 hours.
- Sepsis: life threatening organ dysfunction caused by dysregulated host response to infection [33].
- Septic shock: sepsis with circulatory and cellular/metabolic dysfunction [33].
- Hypotension: systolic blood pressure < 90mmhg and diastolic blood pressure < 60mmhg.

Ethical considerations

Permission to perform the study was granted by the Human Research Ethics Committee of the University of the Witwatersrand (certificate number: M180307)

Table 2. Site of culture.

Site of culture, % (n)	<i>C. auris</i>	<i>C. albicans</i>	<i>C. glabrata</i>
Sterile			
Blood	57.78 (26)	26.67 (12)	48.89 (22)
Tissue	4.44 (2)	6.67 (3)	6.67 (3)
Cerebrospinal fluid	0	0	0
Body fluid*	2.22 (1)	26.67 (12)	11.11 (5)
Bone	2.22 (1)	2.22 (1)	0
Catheter tip	33.33 (15)	13.33 (6)	2.22 (1)
Non sterile			
Urine	20 (9)	24.44 (11)	2.22 (1)
Sputum	0	6.67 (3)	17.78 (8)
Superficial swab	4.44 (2)	0	0
Rectal swab	2.22 (1)	0	2.22 (1)
Tracheal aspirate	0	8.89 (4)	28.89 (13)
Stool	0	2.22 (1)	0

* Body fluid collected during gastro-intestinal surgery.

Results

From 1 January 2015 to 31 August 2018, *C. auris* isolates were identified from clinical specimens of 45 patients, *C. albicans* from 1,959 specimens and *C. glabrata* from 185 specimens. Patient demographics are summarized in Table 1 and site of culture in Table 2. Isolates from more than one site were counted separately, and recorded in Table 2, resulting in higher numbers in Table 2. All *C. auris* infections were HAI, whereas 80% (n = 36/45) of *C. albicans* and *C. glabrata* were HAI. Of the 45 *C. auris* cases, 5 were paediatric (age < 12), and ages ranged from 1 month to 73 years.

Clinical features

Clinical information was available for 41 patients with *C. auris* and all 45 cases of *C. albicans* and *C. glabrata*. Table 3 summarizes clinical features. Fever was more common in the *C. auris* group than in both the other groups (*p* < 0.001). Twelve *C. auris* patients had fever and hypotension. Of these patients, 50% (n = 6/12) had a positive bacterial culture.

Laboratory features

C. auris was cultured from non-sterile sites in 26.66% of cases (n = 12/45). However, 41.67% (n = 5/12) patients concurrently cultured *C. auris* from a sterile site. Fifteen patients cultured *C. auris* from a catheter tip. Of these patients, 40% (n = 6/15) also had positive blood cultures, confirming a catheter-related candidemia.

Table 3. Clinical Features.

	<i>C. auris</i>		<i>C. albicans</i>		<i>C. glabrata</i>		<i>C. auris</i> vs. <i>C. albicans</i>	<i>C. auris</i> vs. <i>C. glabrata</i>
Hypotension, n (%)	N = 41	12 (29.27)	N = 45	10 (22.22)	N = 45	15 (33.33)	<i>p</i> = 0.45	<i>p</i> = 0.68
Altered mental state, n (%)	N = 41	16 (39.02)	N = 45	14 (31.11)	N = 43	17 (39.53)	<i>p</i> = 0.44	<i>p</i> = 0.91
Fever, n (%)	N = 41	28 (68.29)	N = 45	14 (31.11)	N = 45	15 (33.33)	<i>p</i> < 0.001*	<i>p</i> = 0.001*
Temperature spikes, n (%)	N = 28	21 (75)	N = 14	7 (50)	N = 15	1 (6.67)		
Sepsis, n (%)	N = 41	29 (70.73)	N = 45	22 (48.89)	N = 45	224 (53.33)	<i>p</i> = 0.04*	<i>p</i> = 0.1
Septic shock, n (%)	N = 41	11 (26.83)	N = 45	9 (20)	N = 45	12 (26.67)	<i>p</i> = 0.45	<i>p</i> = 0.99

* statistical significance.

Table 4. Laboratory results.

	<i>C. auris</i>		<i>C. albicans</i>		<i>C. glabrata</i>		<i>C. auris</i> vs. <i>C. albicans</i>	<i>C. auris</i> vs. <i>C. glabrata</i>
Haemoglobin [g/dL], mean (IQR)	n = 43	8.3 (7-9.6)	n = 42	9.20 (7.95-11.25)	n = 45	9.20 (9-11.3)	<i>p</i> = 0.014*	<i>p</i> = 0.038*
White cell count [10 ⁹ /L], median (IQR)	n = 43	10.69 (7.69-16.82)	n = 42	13.85 (9-21.21)	n = 45	11.84 (7.13-18.45)	<i>p</i> = 0.092	<i>p</i> = 0.468
Platelet count [10 ⁹ /L], median (IQR)	n = 43	260 (161-351)	n = 42	232 (179.25-342)	n = 44	209 (124.5-341.25)	<i>p</i> = 0.782	<i>p</i> = 0.410
Albumin [g/L], median (IQR)	n = 36	22.50 (20-26.25)	n = 31	26 (22.5-28.5)	n = 37	23 (19-26)	<i>p</i> = 0.127	<i>p</i> = 0.952
Creatinine [μmol/L], median (IQR)	n = 44	83.5 (53.5-269)	n = 42	76.50(52-187.75)	n = 45	93(51-283)	<i>p</i> = 0.638	<i>p</i> = 0.685
C-reactive protein [mg/L], median (IQR)	n = 31	75 (48-214)	n = 34	178 (118-229.5)	n = 39	180 (102.5-246.5)	<i>p</i> = 0.015*	<i>p</i> = 0.030*
CRP [mg/L] without cultured bacterial organisms, median (IQR)	n = 19	61.50 (40-117)	n = 17	159 (118-220)	n = 21	160 (74-229)	<i>p</i> = 0.002*	<i>p</i> = 0.005*
Pro calcitonin [μg/L], median (IQR)	n = 33	3.38 (0.62-39.03)	n = 23	2.77 (1.13-6.36)	n = 29	7.89 (2.14-36.94)	<i>p</i> = 0.549	<i>p</i> = 0.337
PCT [μg/L] without cultured bacterial organisms, median (IQR)	n = 16	1.45 (0.44--5.64)	n = 7	2.43 (0.57-6.92)	n = 14	4.41 (0.98-13.54)	<i>p</i> = 0.175	<i>p</i> = 0.008*
Beta D Glucan [pg/mL], median (IQR)	n = 15	306 (185- 523)	n = 14	298 (119.25-493.75)	n = 17	278 (60-483)	<i>p</i> = 0.827	<i>p</i> = 0.355

* statistical significance.

Table 5. Risk factors for *Candida* infections.

	<i>C. auris</i>		<i>C. albicans</i>		<i>C. glabrata</i>		<i>C. auris</i> vs. <i>C. albicans</i>	<i>C. auris</i> vs. <i>C. glabrata</i>
	N	% (n)	N	% (n)	N	% (n)		
Previous hospitalization	45	8.89 (4)	45	13.33 (6)	45	26.67 (12)	<i>p</i> = 0.502	<i>p</i> = 0.008*
Median number of days from discharge	8 (IQR 6.25-9.75)		13 (IQR 2.25-19.25)		12 (IQR 8-19.5)			
Number of days from admission to positive result, median (IQR)	35 (21-53)		8 (3-19)		8 (2-18)		<i>p</i> < 0.001*	<i>p</i> < 0.001*
Indwelling devices								
Urinary catheter	44	86.36 (38)	45	48.89 (22)	45	57.78 (26)	<i>p</i> < 0.001*	<i>p</i> = 0.007*
Central line	44	95.45 (42)	45	55.56 (25)	45	64.44 (29)	<i>p</i> < 0.001*	<i>p</i> < 0.001*
NGT	43	72.09 (31)	45	35.56 (16)	45	48.89 (22)	<i>p</i> < 0.001*	<i>p</i> = 0.030*
Post op drain	44	29.55 (13)	45	11.11 (5)	45	8.89 (4)	<i>p</i> = 0.058	<i>p</i> = 0.028*
Haemodialysis catheter	43	41.86 (18)	45	13.33 (6)	45	11.11 (5)	<i>p</i> = 0.004*	<i>p</i> = 0.002*
A- line	43	60.47 (26)	45	26.67 (12)	45	37.78 (17)	<i>p</i> = 0.002*	<i>p</i> = 0.037*
TPN	43	51.16 (22)	45	13.33 (6)	45	26.67 (12)	<i>p</i> < 0.001*	<i>p</i> = 0.022*
HIV	45	20 (9)	45	17.78 (8)	45	18.18 (8)	<i>p</i> = 0.788	<i>p</i> = 0.589
CD4, median (IQR)	237 (129-379)		89 (29.5-333)		36 (10-72.5)			
Antibiotic exposure	43	97.67 (42)	44	59.09 (26)	45	66.67 (30)	<i>p</i> < 0.001*	<i>p</i> < 0.001*
Immunosuppressant								
Steroid	42	38.01(16)	45	35.56 (16)	45	33.33 (15)	<i>p</i> = 1.0	<i>p</i> = 0.975
Other immunosuppressant	42	11.90 (5)	45	15.56 (7)	45	6.67 (3)	<i>p</i> = 0.773	<i>p</i> = 0.757
Organ or stem cell transplant	45	4.44 (2)	45	4.44 (2)	45	2.22 (1)	<i>p</i> = 1.0	<i>p</i> = 0.557
ICU admissions	45	97.78 (44)	45	57.78 (26)	45	60 (27)	<i>p</i> < 0.001*	<i>p</i> < 0.001*
Mechanical ventilation	45	82.22 (37)	45	51.11 (23)	45	57.78 (26)	<i>p</i> = 0.002*	<i>p</i> = 0.011*
Surgical procedure	45	77.78 (35)	45	66.67 (30)	45	64.44 (29)	<i>p</i> = 0.239	<i>p</i> = 0.163
Long term care facilities	45	0	45	0	45	0	N/A	N/A
Malignancy	45	4.44 (2)	45	24.44 (11)	45	4.44 (2)	<i>p</i> = 0.007*	<i>p</i> = 1.0
Diabetes	45	8.89 (4)	45	6.67 (3)	45	22.22 (10)	<i>p</i> = 0.694	<i>p</i> = 0.081
Chronic kidney disease	45	17.78 (8)	45	8.89 (4)	45	4.44 (2)	<i>p</i> = 0.215	<i>p</i> = 0.044*

* *p* values significant.

Four of the other nine patients, did not have paired blood cultures done, and five had blood cultures that were negative for *C. auris*. Nine patients cultured *C. auris* from urine samples, of these patients, eight had an indwelling urinary catheter. Table 4 summarizes the results of laboratory investigations within 24 hours of culture collection.

Bacteria were cultured concurrently in 46.67% (n = 21/45) of patients with *C. auris*, 51.11% (n = 23/45) of patients with *C. albicans* and 44.44% (n = 20/45) of patients with *C. glabrata*. Common organisms cultured are shown in Figure 1.

Where candidaemia was suspected, 33.33% (n = 15/45) of patients with *C. auris*, 31.11% (n = 14/45) of *C. albicans* and 37.78% (n = 17/45) of *C. glabrata* patients had a BDG test performed on blood. The overall sensitivity of BDG was 86.67% for *C. auris*, 92.31% for *C. albicans* and 64.71% for *C. glabrata*.

Figure 1. Bacteria cultured concurrently with Candida species.

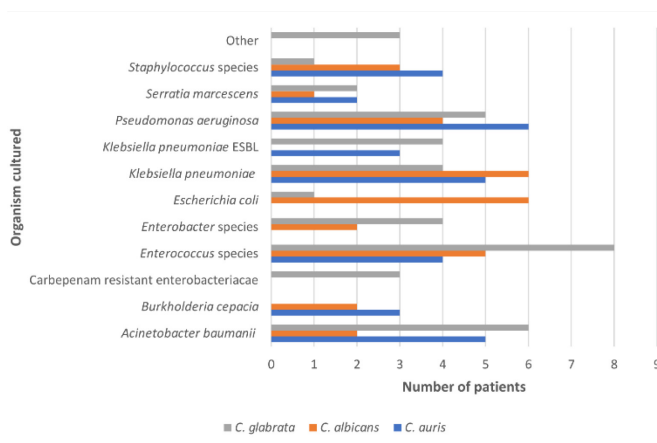
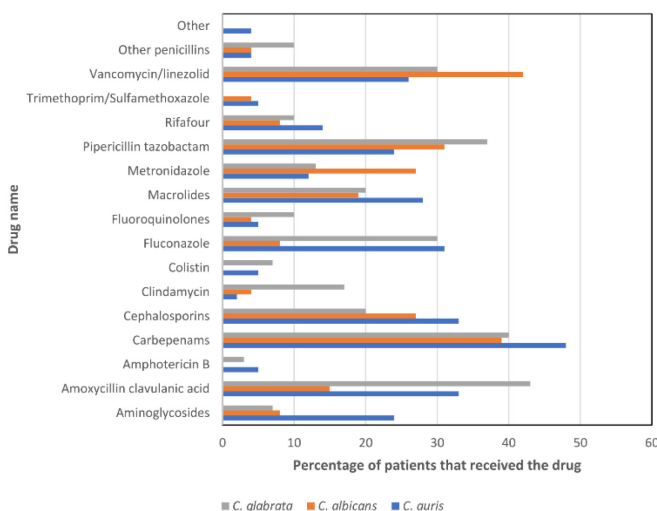


Figure 2. Individual antimicrobials and the percentage of patients that received each drug.



The sensitivity of BDG for isolates cultured from sterile sites only, was 84.62% for *C. auris*, 100% for *C. albicans* and 81.82% for *C. glabrata*.

Forty-one patients had susceptibility results available for *C. auris*, but only 25 patients had MIC data available. All 25 isolates were resistant to fluconazole with high MICs of > 256 µg/mL; MIC₅₀ and MIC₉₀ for voriconazole were 1 µg/mL and 32 µg/mL respectively. All isolates were susceptible to amphotericin B and micafungin with an MIC₅₀ of 0.25 µg/mL and MIC₉₀ of 1 µg/mL for amphotericin B and MIC₅₀ of 0.06 µg/mL and MIC₉₀ of 0.12 µg/mL for micafungin. There were 29 isolates of *C. albicans* with MIC results available. All isolates were susceptible to azoles with a MIC₅₀ of 0.12 µg/mL and MIC₉₀ of 0.25 µg/mL for fluconazole and MIC₅₀ and MIC₉₀ both 0.03 µg/mL for voriconazole. MIC results were available for 26 *C. glabrata* isolates. The MIC₅₀ was 32 µg/mL and MIC₉₀ was 64 µg/mL for fluconazole and 46.15% (n = 12/26) isolates were susceptible to dose dependant fluconazole. The voriconazole MIC₅₀ was 0.25 µg/mL and MIC₉₀ 1 µg/mL. All *C. glabrata* isolates were susceptible to amphotericin B but MICs were not available.

Risk factors

There was an association between indwelling devices and *C. auris* culture, compared to patients with *C. albicans* and *C. glabrata*. Of the *C. auris* patients with indwelling devices, 18 patients had both haemodialysis catheter and central venous lines. Table 5 details the comparative risk factors between the 3 species.

Antimicrobial exposure data is available for 43 patients. In the 30 days prior to infection or colonisation with *C. auris*, 97.67% (n = 42/43) patients received antimicrobials. The percentage of patients that received specific antimicrobials are listed in Figure 2. Prior antimicrobial exposure was significantly associated with *C. auris* infection (p < 0.001). Thirty-five patients, with *C. auris*, underwent a surgical procedure; 57.14% (n = 20/35) had abdominal surgery, 25.71% (n = 9/35) had thoracotomies and 14.29% (n = 5/35) had craniotomies. Repeat/relook surgery was performed in 65.71% (n = 23/35) of surgical patients and 82.61% (n = 19/23) of these patients had multiple (≥ 2) secondary surgical procedures. Surgical procedures were undertaken in 42.86% (n = 15/35) of patients for traumatic injuries, ranging from gunshot wounds to blunt force trauma. Multiple surgery was a significant risk factor in both comparison groups (p = 0.003 for *C. auris* vs. *C. albicans* and p = 0.03 *C. auris* vs. *C.*

glabrata). Of the patients that presented with community acquired *C. albicans* and *C. glabrata*, 66.67% (n = 6/9) of the *C. glabrata* and 55.56% (n = 5/9) of the *C. albicans* patients had perforated gastrointestinal organs with intra-abdominal sepsis.

The majority of *C. auris* cases, 80% (n = 36/45), were cultured during the course of ICU admission, compared to 46.67% (n = 21/45) *C. albicans* and 37.78% (n = 17/45) of *C. glabrata* cases.

Treatment

Treatment data for 43 patients with *C. auris* was available. Fifteen patients (34.89%) were not treated. Seven of these patients died within 1-12 days of the positive culture result. Three of these patients had candidemia, two cultured *C. auris* from CVC tips and two from urine.

Treatment was initiated in 65.12% (n = 28/43) of patients. The median number of days from culture identification of *C. auris* to initiation of treatment was 5 days (IQR = 3.25-7), in both the micafungin and amphotericin B groups. Micafungin was administered to 39.29% (n = 11/28) of patients, of which 54.55% (n = 6/11) died. Three of the 6 patients who died were initially treated with amphotericin B, then switched to micafungin. Amphotericin B was initiated in 63.64% (n = 18/28) of patients. Of the 15 patients treated with amphotericin B alone, 73.33% (n = 11/15) died. The remaining two patients were treated with fluconazole.

Treatment duration was available for only seven patients who survived. The average number of days of treatment was 16.7 days (IQR = 14-17.5). Of the treated patients who died, 11 died while still receiving treatment, with duration of therapy ranging from 1-12 days of treatment. The difference in mortality rate for *C. auris* patients, treated with micafungin versus

amphotericin B, was not statistically significant ($p = 0.32$).

In the *C. albicans* group, 40% (n = 18/45) of patients received treatment, of which 88.89% (n = 16/18) were initiated on fluconazole. Two patients were initiated on amphotericin B then de-escalated to fluconazole. The median time from positive result to treatment initiation was 5 days (IQR = 2-5).

In the *C. glabrata* group, 48.89% (n = 22/45) of patients received treatment. Fluconazole was initiated in 45.45% (n = 10/22) of patients. Susceptibility data was only available for six of these patients, of which four were resistant to fluconazole, and 20% (n = 2/10) were subsequently escalated to amphotericin B. Amphotericin B was administered to 63.64% (n=14/22) of patients and one patient was switched to micafungin. The median time from positive result to commencement of treatment was four days (IQR = 0.25-6). Of the patients treated with fluconazole, 70% (n = 7/10) died and 71.43% (n = 10/14) of patients treated with amphotericin B died.

Outcomes

From the 28 *C. auris* patients that were treated, 39.29% (n = 11/28) patients died prior to completion of treatment, 53.57% (n = 15/28) were successfully treated and 2 patients had incomplete outcome data.

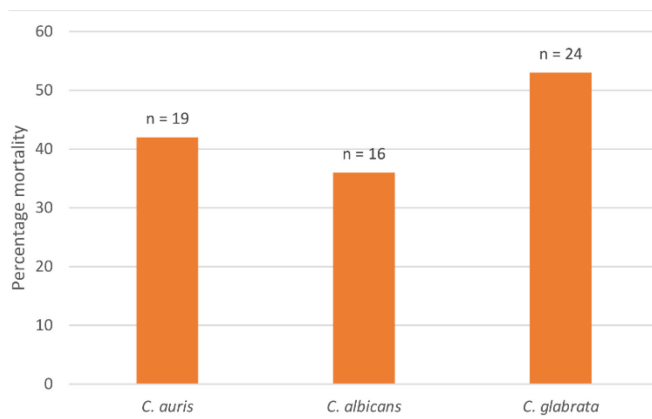
The median number of days from diagnosis of *C. auris* to death was 13 days (IQR = 6.5-34). The median number of days from diagnosis to death for *C. albicans* was 9 days (IQR = 3-18) and for *C. glabrata* 7 days (IQR = 1-14). Of the *C. auris* patients that died, 94.74% (n = 18/19) had ICU acquired infections. The 30-day all-cause in-patient mortality overall is shown in Figure 3. For patients with candidemia, the 30-day all-cause mortality was 57.70% (n = 15/26) in the *C. auris* group, 58.33% (n = 7/12) for *C. albicans* and 77.27% (n = 17/22) for *C. glabrata*. All *C. auris* cases, 80% (n = 36/45) of *C. albicans* and 80% (n = 36/45) of *C. glabrata* cases were hospital acquired.

Of the 26 patients with *C. auris* candidemia, 76.92% (n = 20/26) were treated, 60% (n = 12/20) of these patients died within 30 days. Of the 19.23% (n = 5/26) untreated patients, 60% (n = 3/5) of patients died. The treatment information of one patient was not available. *C. auris* candidemia was ICU acquired in 80.77% (n = 21/26) of cases. Of these cases, 66.67% (n = 14/21) died within 30 days.

Discussion

This study demonstrates that *C. auris* is indeed an emerging threat in South Africa and is associated with

Figure 3. 30-day all-cause in-patient mortality.



ICU admissions. In this cohort, mortality was 42%, which falls within the range of 28-50% in published studies [10,12,14,15].

In this study, more males than females were infected with *C. auris*. This is possibly due to the nature of the underlying pathology, as 33.33% (n = 15/45) of patients were admitted for traumatic injuries requiring surgery, and only one of these patients were female.

A longer length of hospital stay, as well as longer duration from admission to diagnosis was statistically significant in the *C. auris* group compared to the other two *Candida* species. The median time from admission to diagnosis of *C. auris* was 35 days, which was approximately a week longer than in previous studies [14,15]. Median time from admission to diagnosis of *C. glabrata*, in a previous study, was 3.5 days, compared to 8 days in this study [25].

Patients were not routinely screened for *C. auris* colonization on admission. The total number of infected patients that were colonized is unknown. *C. auris* was predominantly (84.44%, n=38/45) cultured from sterile sites which suggests infection rather than colonization. However, it is possible that candidaemia was missed in patients with negative blood cultures as a result of poor sensitivity of blood cultures for *Candida* spp. In addition, biochemical features suggest that, at the time of diagnosis, patients were systemically ill with low median albumin and haemoglobin in all 3 groups.

No specific clinical features were found to be associated with *C. auris* infection. Many patients had a fever, but it is difficult to conclude if the fever was due to *C. auris* alone, or due to the concurrent bacterial infection.

The CRP and PCT in patients that cultured *C. auris* alone (median CRP 61.50 mg/L and PCT 1.45 µg/L) were lower than in patients that cultured bacteria as well (median CRP 75 mg/L and PCT 3.38 µg/L). A study comparing bacterial and fungal infections, found a PCT > 5.5 µg/L was associated with bacterial infections and not candidemia [34]. Median PCT in candidemia was found to be 0.7 µg/L [35], 0.99 µg/L [36] and 0.5 µg/L [37] in 3 different studies. A raised CRP with a low positive PCT may suggest an isolated fungal infection [37,38]. BDG sensitivity was 86.67% for *C. auris*. BDG can be used as an adjunct to other diagnostic assays for fungal infections but cannot be used to distinguish between different *Candida* species [26].

The MIC for amphotericin B in our study was lower than other published studies [12,14,15] but the MIC for micafungin is similar to previous studies [10-12,14]. There was no resistance to amphotericin B or micafungin, but all organisms were resistant to

fluconazole. Despite having a low MIC, patients treated with amphotericin B alone, had a higher mortality (73.33%, n = 11/15) than patients treated with an echinocandin (54.55%, n = 6/11). The causes of mortality in the amphotericin B group were not assessed. We can therefore not conclude, from this study, if the increased mortality was due to poor treatment response, drug toxicity or non *C. auris* related factors.

It is evident that all indwelling devices predispose patients to *C. auris* infection. However, the duration of exposure to the indwelling device was not assessed. HIV co-infection was not a significant risk factor and *C. auris* infection occurred in patients with a high CD4 count. Immunosuppressant use, specifically glucocorticoids, was documented in many patients but was not a statistically significant risk factor for the development of *C. auris*.

Surgical procedures and antimicrobial exposure are risk factors for *C. auris* infections [10,11,15,25]. In this study, the number of repeat surgeries was significantly associated with *C. auris* infection, as was the exposure to antimicrobials.

In this study, 80% of *C. auris* infections were acquired in ICU. Since *C. albicans* and *C. glabrata* cases were matched for ward-type with *C. auris* cases, the high number of these organisms found in ICU is not a true reflection of the *Candida* distribution throughout the hospital.

The findings of this study are limited due to incomplete clinical data, and small sample size. In addition, isolates that were not identified by the microbiology laboratory, and released as 'yeast not *Candida albicans*' or '*Candida* species' may have been missed *C. auris* isolates. Matching of *C. albicans* and *C. glabrata* patients was performed manually and may have resulted in some bias. In addition, cases should have been matched for site of infection first, with a particular focus on bloodstream infections. A control group with no candidemia was not included to compare clinical findings and risk factors, thus the data provided here may be partial. The incidence of candidaemia at this hospital was not calculated. Information regarding inter hospital transfer or recent admission to other hospitals was not collected. Appropriateness of antifungal dosing was not assessed. No data was collected to evaluate source control. There are multiple confounding factors affecting the mortality rate, especially severity of the underlying illness, which have not been addressed in this study.

Conclusions

At CMJAH, *C. auris* is a healthcare associated pathogen specifically associated with ICU admission, increased length of hospitalisation, broad spectrum antimicrobials and indwelling devices. Diagnosis in this setting may be assisted by non-culture based assays such as the BDG in combination with inflammatory markers such as the CRP and PCT, but may only be valuable in cases where no concomitant bacterial infection is present.

Considering the high mortality rate associated with this MDR pathogen, it is imperative that intensive infection control measures are implemented to prevent horizontal transmission of *C. auris*. Equally important is a commitment to robust antimicrobial stewardship in order to curb resistance and emergence of further multidrug resistant pathogens.

Authors' contributions

Amirah Parak was the principal investigator and primary author of the protocol and final manuscript. Sarah Stacey and Vindana Chibabhai conceptualised the study and assisted with study design, editing and approving of the final manuscript.

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