A research report
submitted to the University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine 2020.

TITLE:

Disease profile and outcomes of patients with *Candida auris* infections, compared to other *Candida* species, at a tertiary South African Hospital.

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DECLARATION

I, Amirah Parak, declare that this research report is my own unaided work. The research report is being submitted for the degree Master of Medicine, in Internal Medicine, at the University of Witwatersrand, Johannesburg. It is being submitted in the submissible format, with my protocol and an extended literature review. It has not been submitted before, for any degree or examination, at this or any other University.

Amirah Parak

Signed 03 day of March 2020

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PRESENTATIONS/PUBLICATIONS ARISING FROM THIS PROJECT

Nil at time of submission.

ABSTRACT

Introduction

Multidrug resistant *Candida auris* is a novel and emerging threat worldwide. It has been identified in Africa, however, there is not enough data available comparing *C. auris* to other *Candida* species found in Africa.

Objective

To compare the clinical and laboratory features, risk factors, treatment and outcome of *C. auris* to the most virulent *Candida* species (*Candida albicans*) and a well-known azole resistant *Candida* species (*Candida glabrata*).

Method

Retrospective, cross-sectional, analysis of all patients with a positive culture for *C. auris* , from 1 January 2015 to 31 August 2018, at a tertiary South African Hospital. An equal number of patients with *C. albicans* and *C. glabrata* were matched for comparison.

Results

Forty-five cases of *C. auris* infection were identified. The median age was 32 years (IQR 26-46) with 71.1% (n=32/45) being male. Median duration of hospital stay for *C. auris* was 64 days (IQR 39-88) and median time from admission to diagnosis was 35 days (IQR 21-53), both of which were significant compared to *C. albicans* and *C. glabrata* ($p<0.001$). Indwelling devices, previous antibiotic exposure and multiple surgical procedures were found to be significant risk factors. All *C. auris* isolates were healthcare associated with 80% (n=36/45) acquired in ICU. ICU admission was found to be a significant risk factor. There were no *C. auris* isolates resistant to amphotericin B or micafungin. Despite isolates having a low amphotericin B 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 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*.

Conclusion

C. auris is an emerging multi drug resistant threat in South Africa. Improved access to echinocandins in the public sector is needed for the treatment of *C. auris* infections. In addition,

implementation of improved infection prevention and control strategies are imperative to prevent this multi-drug resistant pathogen from becoming endemic in South Africa.

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ABBREVIATIONS

- BDG- Beta-D-Glucan
- CDC- Centers for Disease Control and Prevention
- CMJAH- Charlotte Maxeke Johannesburg Academic Hospital
- CRP- C reactive protein
- CVC- Central venous catheter
- ICU- Intensive care unit
- MALDI-TOF MS- Matrix-assisted laser desorption ionization–time of flight mass spectrometry
- MDR- Multi drug resistant
- MIC- Minimum inhibitory concentration
- NGT- Nasogastric tube
- NICD- National Institute of Communicable Disease
- NHLS- National Health Laboratory Service
- PCT- Procalcitonin
- TPN- Total parenteral nutrition

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. Background

1.1. *Candida* species epidemiology

Candida species are commensals found on the skin and mucosal surfaces. In patients who are immunocompromised they have the potential to progress to infection[1,2].

Candida species are a common cause of healthcare associated infection, specifically blood stream infections[3]. The EPIC 11 trial found that 17% of intensive care unit (ICU) infections were due to *Candida* species. In addition, *Candida* species were the third commonest cause of ICU infections[4]. Historically, *Candida albicans (C. albicans)* was the commonest *Candida* species causing disease, however in recent years non-*albicans candida* (NAC) have emerged as an important cause of disease[5,6].

There is a paucity of recent data for candidemia in South Africa. A study conducted at Chris Hani Baragwanath Hospital, in 3 periods from 1990 to 2007, found that *C. albicans* was the most common *Candida* species causing candidemia. This was followed by *Candida parapsilosis* and *Candida glabrata (C. glabrata)*[7]. An international study assessing global trends in *Candida* distribution, between 1992 and 2001, found that *C. albicans* caused 81% of candidemia in South Africa, followed by *C. glabrata* at 10%[8]. In a study conducted in the Eastern Cape of South Africa, it was found that the commonest *Candida* species isolated was *C. albicans* followed by *C. glabrata*[9]. Therefore these 2 organisms were chosen to compare with *Candida auris* (*C. auris)* in this study.

1.2. *Candida auris* epidemiology

C. auris was first described in Japan in 2009. It was isolated from the external ear canal of a 70 year old patient[10]. Since 2009 it has been identified in Kuwait[11], South Africa[12], India[13-15], the United States[16], Venezuela[17], Colombia[18], Europe[19] and Israel[20], amongst other countries[21].

C. auris represented 8.6% of annual candidemia cases in an Indian tertiary hospital. *C. auris* was isolated from blood cultures, central venous catheter (CVC) tips, surgically excised tissues, bronchoalveolar lavage fluid and pus, demonstrating that *C. auris* causes

a variety of infections[14].

An Indian study at a tertiary care hospital, *C. auris* represented 30% of yearly candidemia cases, overall, and 5% of the paediatric cases[13].

In Colombia, it was found that the average number of days between hospitalisation and identification of *C. auris* infection was 27.5 days[18]. The mean time from admission to development of candidemia was 24 days in a study conducted in Venezuela[17], suggesting that *C. auris* infection is most likely healthcare associated.

GERMS South Africa candidemia surveillance from January 2016 to September 2017 showed that 11% of cases with candidemia were due to *C. auris*, and 94.2 % of cases were detected in Gauteng[22]. In addition, a study conducted between October 2012 and November 2016, of *C. auris* in South Africa, it was found that 92% of cases of *C. auris* were identified in the Gauteng province[23].

1.3. Laboratory identification

The prevalence of *C. auris* is most likely underestimated globally, as *C. auris* is difficult to identify with standard laboratory methods[21].

C. auris isolates were previously misidentified as *Candida haemulonii (C. Haemulonii)* or other non-albicans *Candida* species by commercial identification systems. A study conducted in India looked at 102 isolates, 100 identified as *C. haemulonii* and 2 as *Candida famata*, by Vitek 2® (BioMérieux, France). These 102 isolates were reviewed using Internal Transcribed Spacer region (ITS) analysis and Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS). Of these 102 isolates, 88.2% (n=90) were identified as *C. auris*. MALDI-TOF MS is considered a more successful modality to identify *C. auris*[24]. Recently, a software upgrade to the Vitek 2® (BioMérieux, France) has allowed for accurate identification of *C. auris.*

Beta-D-glucan (BDG) (positive result >80 pg/ml) was found to be more sensitive than blood cultures in diagnosing deep seated fungal infections from *C. albicans* and *C. glabrata.* However, no data is available for *C. auris* specifically[25].

1.4. Pathogenicity

Biofilm formation is important in the pathogenicity of *C. auris*. It adheres to hospital surfaces, which allows it to survive in hospital environments for prolonged periods, thus contributing to protracted outbreaks. Chlorhexidine is effective against biofilm caused by *C. auris*. The biofilm forming capacity of *C. auris* was tested against those of *C. albicans* and *C. glabrata*. Although *C. albicans* forms more extensive biofilm, the virulence of *C. auris* was comparable to *C. albicans*. It was found that fluconazole was ineffective against both planktonic and sessile *C. auris* with minimum inhibitory concentration (MIC) >32 mg/l. It was found that although voriconazole, caspofungin and micafungin have effect on planktonic *C. auris*, they all exhibit MICs of >32mg/l for sessile/biofilm *C. auris*. Amphotericin B and liposomal amphotericin B exhibit MICs between 2-16mg/l for sessile *C. auris*[26].

1.5. Risk factors

Table 1: Risk factors for acquisition of *C. auris* (%)

Country	Year	CVC	DM	CA	CKD	TPN	UC	Surg	Neutro	ICU	AB	Post - op drain	AF
India-tertiary hospital[14]	2011-2013	83.3	55.5	33.3	44.4	66.6	91.6	58.3	16.7		100		41.6
India[13]	2009-2011	42	50	17	42		83		50	58	75		
India ICU[15]	2011-2012	71.6		8.1		20.3	75.7		2.7	100		33.8	
Colombia[18]	2016	94.1	17.6	11.7	29.4	47	88.2	41.1			88.2		70.6
Venezuela[17]	2012-2013	100						55.6		100			

CVC- central venous catheter
DM-diabetes mellitus
CA- carcinoma
CKD- chronic kidney disease
TPN- total parenteral nutrition
UC- urinary catheter
Surg- surgery (preceding)
Neutro- neutropenia
ICU- intensive care unit
AB- antibiotic (broad spectrum)
AF- antifungal (preceding)

Table 1 is a comparison of proposed risk factors for the acquisition of *C. auris.* The presence of an indwelling catheter, specifically a central venous catheter, has been found in a significant number of patients infected with *C. auris*. Immunosuppressive states, including diabetes

mellitus, underlying malignancy, chronic kidney disease and neutropenia have been identified as predisposing factors for the acquisition of *C. auris* infection. A consistent finding in all studies was the presence of a urinary catheter. In table 1, 41.1% to 58.3% of *C. auris* infected patients had a surgical procedure prior to infection with *C. auris*.

A study looking at candidemia over a decade (not specifically *C. auris*), found that surgery (predominantly abdominal) had been performed 30 days prior to the diagnosis of candidemia in 36.3% of patients[27]. Prior use of immunosuppressive drugs was seen in 23.1% of patients[27].

In table 1, prior antibiotic administration was found in a greater percentage of patients as opposed to prior antifungal use. However, only two studies assessed previous antifungal exposure. In a study looking at antibiotic exposure, preceding antibiotic exposure within 30 days of diagnosis was associated with candidemia. Specific drug classes associated with fluconazole-resistant *Candida* blood stream infections include carbapenems, clindamycin, colistin, trimethoprim-sulfamethoxazole and all antifungal agents. Metronidazole specifically predisposed to *C. glabrata* infection[28].

In the GERMS South Africa surveillance, risk factors were found to be prior hospital admission, increased length of stay prior to first positive blood culture, mechanical ventilation and prior systemic antimicrobial use[22].

1.6. *C. auris* versus other *Candida* species

Duration of ICU stay before candidemia diagnosis was longer in patients with *C. auris* compared to other species (*C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. krusei* and *C. glabrata*). Prior antifungal exposure was higher in patients infected with *C. auris* compared to *C. albicans* and *C. tropicalis*. TPN and longer indwelling CVC were found in more patients with *C. auris* than patients infected with other *Candida* strains. Other associations found with *C. auris* infection (versus other *Candida spp.*) were low acute physiology and chronic health evaluation II (APACHE II) score, concomitant respiratory illness and vascular surgery[15].

A study conducted in the United Kingdom compared the pathogenicity of *C. auris* to other common pathogenic *Candida spp*. *C. albicans* has been found to be the most virulent of the *Candida spp*. The study found that *C. auris* virulence was comparable to *C. albicans*[26].

Median number of days from admission to detection of *C. glabrata* was 3.5 days (Range 0.8-13)[27]. The same study found that 40% of *C. glabrata* isolates were resistant to fluconazole.

1.7. Screening and precautions

C. auris has a propensity to cause outbreaks, therefore it is very important to be able to identify it early and institute early treatment. The Centers for Disease Control and Prevention (CDC) and National Institute for Communicable Diseases (NICD) recommends screening of contacts for colonization, isolation of patients with *C. auris*, environmental disinfection with hospital grade disinfectant and application of strict contact precautions[21,29]. Screening involves swabbing the groin and axilla of close contacts. However, colonization may also occur in the rectum, wounds, urine, oropharynx, nose and external ear canal. As of 2019, the CDC has listed *C. auris* as a notifiable condition[21].

An outbreak in an ICU in Europe prompted environmental investigation for *C. auris*. It was found that horizontal surfaces around an infected patient's bed were contaminated by *C. auris* (the floor, windowsills, trolleys etc). Two hundred and fifty-eight health care workers were swabbed for *C. auris*. This yielded only 1 positive nose swab out of 258. Patients were also swabbed for colonization. Twice daily chlorhexidine washes were prescribed for *C. auris* colonized patients. The rooms were cleaned with chlorine-based disinfectant three times daily and intensively on discharge. For a period of one year, during the outbreak, all patients admitted were screened for *C. auris* colonization. The prevalence of *C. auris* colonization was found to be negligible at 0.04%[19].

The NICD recommends cleaning of patients' rooms with a chlorine releasing agent with a strength of 1000 ppm and terminal cleaning with hydrogen peroxide vapour[29]. The CDC recommends that Environmental Protection Agency (EPA) registered hospital grade disinfectants effective against *C. difficile* be used against *C. auris*[21]. A study tested both EPA approved disinfectants, as well as hydrogen peroxide disinfectants and found them active against *C. auris* and other *Candida* species[30,31].

1.8. Treatment options and resistance profile

The CDC and Public Health England (an executive agency of the Department of Health in the United Kingdom) guidelines recommend echinocandins as first-line treatment for *C. auris*[21,32]. The South African NICD recommends echinocandins or amphotericin B as first

line therapy. Echinocandins however, do not achieve high urine concentrations. Therefore, amphotericin B is recommended in patients with urinary tract infection. The removal of all indwelling lines and catheters is advised[29]. There is currently no evidence based recommendation for combination therapy to treat invasive *C. auris* infections. Looking at the table below, it is concerning that some isolates have high MICs to caspofungin and amphotericin B.

Table 2: MIC range (mg/l) of various antifungal agents against *C. auris*

Country	Year	Fluc	Vor	Pos	Isa	Itra	Ampho B	Flu	Cas	Mica	Anid
India- tertiary hospital[14]	2011-2013	64	0.5-4	0.015 - 0.125	0.06-4	0.06-0.25	0.25-1	0.25-64	0.25-1	0.06-0.125	0.125 -0.25
India-2 hospitals[13]	2009-2011	16-64	0.12 5-1	0.06-0.25	<0.01 5-0.25	0.125 -0.25	0.25-1	0.125	0.125 -0.25	0.06-0.125	0.125 -0.5
India- ICU[15]	2011-2012	0,12 -64	0.03-4	0.03-2		0.03-2	0.06-8		0.12-4	0.03-2	0.03-2
Colombia[18]	2016	16-64	<0.1 2-2				8-16		<0.25 -0.5	<0.06 -0.25	
Venezuela[17]	2012-2013	>64	4				1-2	0.5			0.06-0.125
South Africa[12]	2012-2013	64-256	0.25-2	0.015 -0.06		0,06-0,25	0.5-1	0.06-0.12	0.03-0.25	0.06-0.12	0.06-0.25

*Fluc-fluconazole Vor-voriconazole Pos-posaconazole
Isa- isavuconazole Itra- itraconazole Ampho B-amphotericin B
Flu- flucytosine Cas- caspofungin Mica- micafungin
Anid- anidulafungin

From table 2, it is evident that the MIC for fluconazole is high globally. In a tertiary Indian hospital, 75% of patients receiving fluconazole developed persistent fungemia[13]. In another Indian study, breakthrough fungemia was observed in 28.6% of patients and therapeutic failure (attributed to initial treatment with fluconazole) was seen in 66.7% of patients[14].

A meta-analysis of 742 *C. auris* isolates globally found the resistance profile to be as follows: 44.29% fluconazole, 15.46% amphotericin B, 12.67% voriconazole, 3.48% caspofungin, 1.95% flucytosine, 1.25% anidulafungin, 1.25% micafungin[33].

There are currently no established susceptibility breakpoints for *C. auris*. The CDC provides a guideline to MIC based on similar organism:[21]

- Fluconazole MIC ≥32 µg/ml
- Amphotericin B ≥2 µg/ml
- Micafungin and Andulafungin ≥4 µg/ml
- Caspofungin ≥2 µg/ml

1.9. Mortality

Table 3: Mortality rates of patients infected with *C. auris* (%)

Country	Number of patients in study	Year	Mortality %
India[13]	12	2009-2011	33-50
India- ICU[15]	74	2011-2012	41.9 crude 27 attributable
Colombia[18]	17	2016	35.2
Venezuela[17]	18	2012-2013	28

2. Justification for the Study

Since 2009 there have been multiple outbreaks of *C. auris*. It is an extremely difficult organism to identify as well as being multi-drug resistant. In order to curb outbreaks, we need to understand the risk factors related to transmission as well as the resistance pattern of the organism in South Africa. Echinocandins are the first line treatment for *C. auris*. Unfortunately, they are not freely available in South African public hospitals. We therefore need to review the outcome of patients treated with other antifungal agents. *C. albicans* is the "prototype" *Candida spp.* causing invasive disease and is regarded as the most virulent of *Candida spp*. It is however quite a susceptible species. *C. glabrata* is becoming more prevalent in South Africa but is resistant to azole antifungals. The study will therefore compare *C. auris* to the most virulent species (*C. albicans*) as well as an azole resistant *Candida* (*C. glabrata*).

3. Aim

To determine the demographics, disease profile and treatment outcomes of patients diagnosed with *Candida auris* infection at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

4. Objectives

4.1. To determine the demographics, clinical presentation and risk factors of patients with *C. auris*, and compare these with an equal number of patients infected with *C. albicans* and *C. glabrata* during the study period.

4.2. To determine the site of infection and laboratory features related to sepsis/organ dysfunction (haemoglobin, white cell count, C- reactive protein, PCT, albumin, renal function, beta-D-glucan) associated with *C. auris, C. albicans* and *C. glabrata* infection.

4.3. To determine if infection control measures were instituted i.e. barrier nursing, patient isolation.

4.4. To determine the treatment instituted, MIC values of the antifungal agents, and patient outcome based on treatment regimen.

4.5. To determine the 30 day all-cause, in-patient mortality rate of patients infected with *C. auris*, *C. albicans* and *C. glabrata.*

5. Method

5.1. Study setting:

The study will be conducted at Charlotte Maxeke Johannesburg Academic hospital.

5.2. Study period:

1 January 2015 to 31 August 2018.

5.3. Study design:

Retrospective case analysis of laboratory confirmed cases of *C. auris*, *C. albicans* and *C. glabrata.* A record of patients will be obtained from the National Health Laboratory Service (NHLS) database. Patients' bed-letters/inpatient notes will be reviewed to extract data regarding demographics, treatment and outcomes. Data will be entered onto an anonymous data capture sheet. (Appendix A)

5.4. Study population:

All patients who cultured *C. auris,* from a clinical specimen at CMJAH during the study period, as well as, an equal number of patients with *C. albicans* and *C. glabrata* who have been matched for age and ward type.

5.5. Inclusion criteria:

All patients diagnosed with *C. auris* during the study period and an equal number of patients with *C. albicans* and *C. glabrata* matched by age and ward type.

5.6. Exclusion Criteria:

i. Duplicate isolates

ii. Patients for whom bed-letters cannot be found.

5.7. Measurement tool:

The measurement tool for data collection will be data capture sheets (Appendix A).

5.8. Source data:

TrakCare report of patients with *C. auris*, *C. albicans* and *C. glabrata* will be obtained from CMJAH NHLS Microbiology Laboratory (with permission). In addition, patient bed-letters and associated admission documentation will be obtained from CMJAH records.

5.9. Study definitions:

i. Healthcare associated infection- infections occurring more than 48 hours after hospitalization.

ii. ICU acquired candidiasis- culture of *Candida* species obtained 48 hours after ICU admission or within 48 hours after discharge from ICU.

iii. Antifungal exposure- empiric or prophylactic therapy with antifungal agents up to 30 days prior to the diagnosis of candidiasis.

iv. Outcome- determined 30 days after onset of candidiasis.

v. Persistent fungemia- culture persistently positive after 14 days of appropriate antifungal therapy and source control.

vi. 30 day all-cause in-patient mortality- number of patients who died, whilst still inpatients within 30 days of onset of candidiasis, regardless of cause of death.

5.10. Limitations and bias of the study

i. Acquisition of patient bed-letters is not always possible.

ii. All required information may not be documented adequately in the bedletters/admission notes.

iii. Each doctor's clinical assessment is different and no standardization can be implemented.

5.11. Data Processing and Data analysis

Each patient will be allocated a unique study number. No patient identifiers will be used. The data will be entered into an Excel spread sheet and analysed using descriptive statistical methods. Data will be presented as mean and standard deviation if normally distributed or median and range if not normally distributed. Comparison of continuous variables will be

done by the t-test and categorical data by the Chi-squared test. Statistical significance will be calculated at the 95% confidence interval. A consort diagram will be included to illustrate patient numbers and if data collection for each patient was complete or incomplete.

6. Ethics

6.1. No patient identifiers will be used. All patients will be allocated a unique study number.

6.2. The study proposal will be submitted to the Postgraduate Committee of the University of the Witwatersrand and the Human Research Ethics committee (HREC) of the University of the Witwatersrand in order to get approval for the study.

6.3. All information will be obtained personally from the patient's files/bed-letters.

6.4. Consent will be obtained from the head of the Department of Internal Medicine, NHLS as well as the CEO of CMJAH.

7. Timeline

	Nov '17	Dec '17	Jan '18	Feb '18	Mar '18	Apr '18	May '18	June '18	July '18	Aug '18	Sep '18	Oct '18
Literature Review												
Preparing protocol												
Protocol assessment by supervisors												
Ethics Application												
Post graduate assessment												
Refine protocol												

Collecting Data											
Data Analysis											
Write up											

8. Funding

The cost for stationary and photocopying, which is estimated at R1000, will be self-funded.

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CHAPTER 2: SUBMISSABLE ARTICLE

Disease profile and outcomes of patients with *Candida auris* infections, compared to other *Candida* species, at a tertiary South African Hospital.

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- **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.
- **Disclosure:** No conflict of interest.

Abstract

Introduction

Multidrug resistant *Candida auris* is a novel and emerging threat worldwide. It has been identified in Africa, however, there is not enough data available comparing *C. auris* to other *Candida* species found in Africa.

Objective

To compare the clinical and laboratory features, risk factors, treatment and outcome of *C. auris* to the most virulent *Candida* species (*Candida albicans*) and a well-known azole resistant *Candida* species (*Candida glabrata*).

Method

Retrospective, cross-sectional, analysis of all patients with a positive culture for *C. auris* , from 1 January 2015 to 31 August 2018, at a tertiary South African Hospital. An equal number of patients with *C. albicans* and *C. glabrata* were matched for comparison.

Results

Forty-five cases of *C. auris* infection were identified. The median age was 32 years (IQR 26-46) with 71.1% (n=32/45) being male. Median duration of hospital stay for *C. auris* was 64 days (IQR 39-88) and median time from admission to diagnosis was 35 days (IQR 21-53), both of which were significant compared to *C. albicans* and *C. glabrata* ($p<0.001$). Indwelling devices, previous antibiotic exposure and multiple surgical procedures were found to be significant risk factors. All *C. auris* isolates were healthcare associated with 80% (n=36/45) acquired in ICU. ICU admission was found to be a significant risk factor. There were no *C. auris* isolates resistant to amphotericin B or micafungin. Despite isolates having a low amphotericin B 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 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*.

Conclusion

C. auris is an emerging multi drug resistant threat in South Africa. Improved access to echinocandins in the public sector is needed for the treatment of *C. auris* infections. In addition,

implementation of improved infection prevention and control strategies are imperative to prevent this multi-drug resistant pathogen from becoming endemic in South Africa.

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 infections, especially blood stream infections[3,4]. In the past, *Candida albicans* was the predominant cause of infection, however, there has been a shift towards non-*albicans Candida* species (NAC) causing disease[5,6]. *Candida auris* is an emerging *Candida* species that causes healthcare associated infections. *C. auris* was first identified in 2009, from the external ear canal of a patient in Japan[7]. It has since been identified in South American countries, the United States, Europe and South Africa, amongst many other countries[8-18].

Prior to 2016, 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 *Candida* species followed by *C. albicans.* It also found that *C. auris* was the fourth commonest *Candida* causing disease[22]. Eleven percent of candidemia in South Africa was due to *C. auris* in 2016-2017 and 94.2% of these cases were identified in the Gauteng province[23,24].

Length of hospitalisation prior to infection appears to differ between species. It was found that the average number of days between hospitalization and identification of *C. auris* infection was 24 days[14] and 27.5 days[15] in two different studies. The median number of days from admission to detection of *C. glabrata* was 3.5 days (range 0.8-13)[25]. In a previous study of 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].

The detection of Beta-D-glucan (BDG) is found to be more sensitive than blood culture for the diagnosis of deep-seated *Candida* infections due to *C. albicans* and *C. glabrata*. However, minimal information is available regarding the sensitivity of BDG for diagnosis of invasive *C. auris* infection[26].

Known risk factors for acquisition of *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[10,11,12,14,15,23,27]. 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]. A meta-analysis of 742 *C. auris* isolates, globally, reports the resistance profile to be as follows: 44.29% fluconazole, 15.46% amphotericin B, 12.67% voriconazole, 3.48% caspofungin, 1.95% flucytosine, 1.25% anidulafungin, 1.25% micafungin[28]. However, in a study performed in India, all isolates were resistant to fluconazole and 73% were resistant to voriconazole[11]. Based on these susceptibility data, the CDC and Public Health England recommend echinocandins as first line treatment. The NICD recommends echinocandins as first line treatment for all patients above 2 months of age. However, for eye, urinary tract or central nervous system infections, as well as children younger than two months, amphotericin B is recommended[18,29,30]. Globally, echinocandins are recommended as first line treatment but the South African public sector has minimal, if any, access to liposomal amphotericin B and echinocandins.

Aim of the study

Globally, little information is available on *C. auris* compared to other *Candida* species. *C. albicans* is the prototypical *Candida* species and regarded as the most virulent. *C. glabrata* is a well-known azole resistant *Candida* species. *C. auris* has been found to be as virulent as *C. albicans*[31] as well as multidrug resistant[28]. The study will therefore compare clinical features, risk factors and outcomes of *C. auris,* to the most virulent species (*C. albicans*), as well as an azole-resistant species, namely *C. glabrata*.

Methods and study design

i. Study population and study design

This retrospective, cross-sectional, study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary 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 (provided they were cultured within the same admission) were counted as a single case. The corresponding number of patients with *C. glabrata* and *C. albicans* were chosen by ward, age and if possible, site of culture. It was, however, not possible to match age exactly for each patient. Therefore, patients with the closest age (within a 10-year range) were included.

ii. Microbiological methods

Routine culture medium was used to culture *C. auris*. The Vitek 2® (bioMerieux, Marcy-L'Etoile) 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® BDG assay (Associates of Cape Cod, Massachusetts) is used at the NHLS. Fungitell® results <60 pg/ml were reported as negative, 60-80 pg/ml as equivocal and >80 pg/ml as positive.

iii. Data collection

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

iv. Statistical analysis

Each group of organisms was analysed separately. 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. Odds ratios were calculated for factors associated with mortality. The Haldane-Anscombe correction was applied to the odds ratio if one of the variables was zero.

v. Study definitions

i. Healthcare associated infection- a positive *Candida* culture, more than 48 hours after admission, associated with clinical or laboratory features of infection.
ii. ICU acquired candidiasis- Culture of *Candida* species obtained 48 hours after ICU admission or within 48 hours of discharge from ICU.
iii. Antifungal exposure- empiric or prophylactic therapy with an antifungal agent up to 30 days prior to the diagnosis of candidiasis.
iv. Antibiotic exposure- empiric or prophylactic therapy with an antibiotic up to 30 days prior to the diagnosis of candidiasis.
v. Outcome- determined 30 days after the diagnosis of candidiasis.
vi. 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.
vii. Temperature spikes- An intermittent sharp rise in body temperature, with resolution to baseline. These intermittent increases in temperature lasted between 24 and 48 hours.
viii. Sepsis- life threatening organ dysfunction caused by dysregulated host response to infection[33].
ix. Septic shock- Sepsis with circulatory and cellular/metabolic dysfunction[33].
x. Hypotension- systolic blood pressure < 90mmhg and diastolic blood pressure <60mmhg.

vi. Ethical considerations

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number: M180307). Permission was obtained from the NHLS for acquisition of data, Department of Internal medicine at CMJAH and the Chief executive officer of CMJAH. The protocol was also entered into the South African Department of Health National Health Research Database (Reference GP_201806_047).

Results

i. Overall

From 1 January 2015 to 31 August 2018, *C. auris* isolates were identified from clinical specimens of 45 patients. Demographics are summarized in table 1 and site of culture in table 2. Some patients cultured candida from multiple sites. If a patient cultured Candida from more than one site, each cultured isolate was counted separately, and recorded in Table 2. Therefore, the number of isolates are more than the number of patients. All *C. auris* infections were healthcare associated, whereas 80% (n=36/45) of both *C. albicans* and *C. glabrata* were healthcare associated. Of the 45 *C. auris* cases, 5 were paediatric (age <12), and ages ranged from 1 month to 73 years.

Table 1: Patient demographics

	C. auris	***C. albicans***	***C. glabrata***	***C. auris* vs *C. albicans***	***C. auris* vs *C. glabrata***
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%)	p=0.186	p=0.267
Total length of hospital stay (days), median (IQR)	64 (39-88)	27 (14-37)	21 (12-44)	**p<0.001**	**p<0.001**

Figures in **bold** indicate statistical significance.

ii. 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 ($p < 0.001$). Of the *C. auris* patients, 50 % (n=6/12) with a fever and hypotension, cultured bacteria as well.

Table 2: Site of culture

	C. auris	*C. albicans*	*C. glabrata*
Site of culture, %(n)			
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.

Table 3: Clinical Features

	C. auris		*C. albicans*		*C. glabrata*		*C. auris* vs *C. albicans*	*C. auris* vs *C. glabrata*
Hypotension, n (%)	N=41	12 (29.27)	N=45	10 (22.22)	N=45	15 (33.33)	p=0.45	p=0.68
Altered mental state, n (%)	N=41	16 (39.02)	N=45	14 (31.11)	N=43	17 (39.53)	p=0.44	p=0.91
Fever, n (%)	N=41	28 (68.29)	N=45	14 (31.11)	N=45	15 (33.33)	**p<0.001**	**p=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)	**p=0.04**	p=0.1
Septic shock, n (%)	N=41	11 (26.83)	N=45	9 (20)	N=45	12 (26.67)	p=0.45	p=0.99

Figures in **bold** indicate statistical significance.

iii. 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. Of the patients who cultured *C. auris* from a catheter tip, 40% (n=6/15) also had positive blood cultures, confirming a catheter-related candidemia. Of the other nine patients, four did not have paired blood cultures done, and five had blood cultures that were negative for *C. auris.* Of the nine patients who cultured *C. auris* from urine samples, eight patients had an indwelling urinary catheter and the information of the ninth patient was unknown.

Table 4 summarizes the results of laboratory investigations done within 24 hours of the positive culture result. Very few patients had a neutrophil count measured with the total white cell count, therefore neutrophil count was not assessed.

Bacteria were cultured from clinical samples 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 (Figure 1) were multidrug resistant *Acinetobacter baumanii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus species, Serratia marcescens, Burkholderia cepacia* complex*, Escherichia coli, Enterococcus faecium* and *Enterococcus faecalis.*

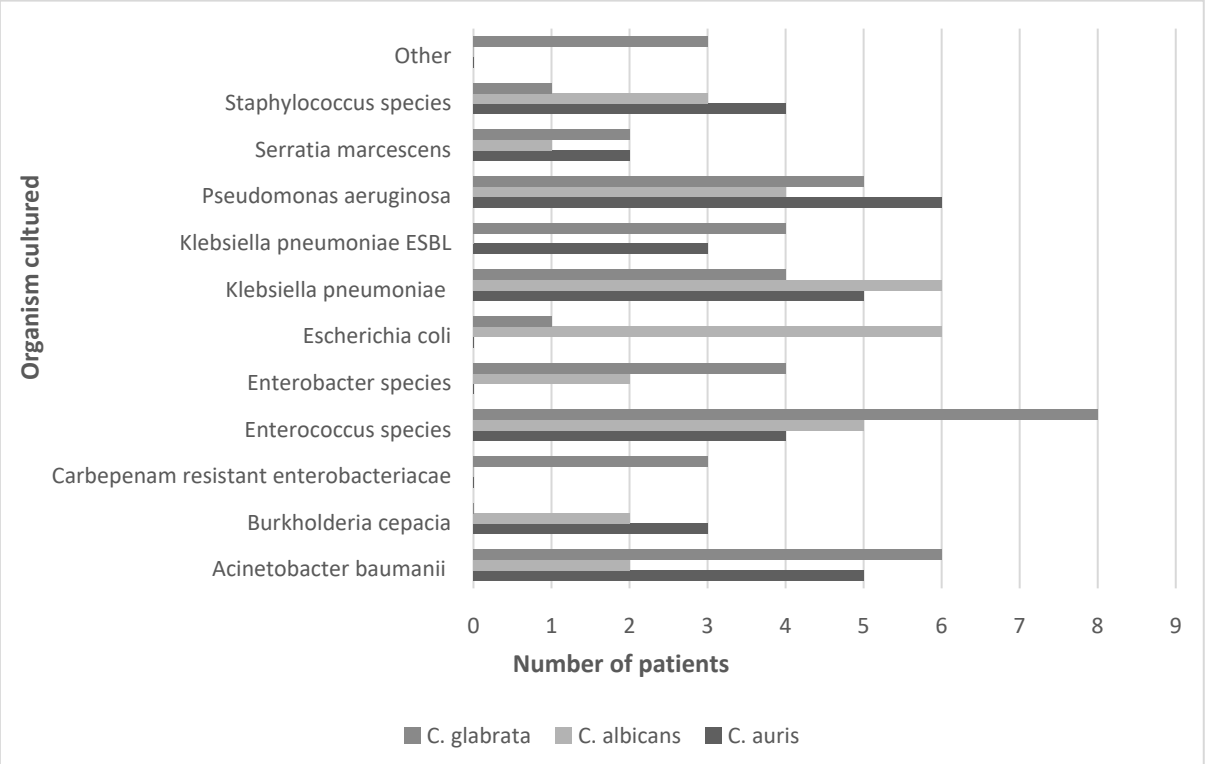

Figure 1: Bacteria cultured concurrently with *Candida* species.

Only 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*. 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; MIC_{50} and MIC_{90} for voriconazole were 1 µg/ml and 32 µg/ml respectively. All isolates were susceptible to amphotericin B and micafungin with an MIC_{50} of 0.25 µg/ml and MIC_{90} of 1 µg/ml for amphotericin B and MIC_{50} of 0.06 µg/ml and MIC_{90} 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 MIC_{50} of 0.12 µg/ml and MIC_{90} of 0.25 µg/ml for fluconazole and MIC_{50} and MIC_{90} both 0.03 µg/ml for voriconazole. MIC results were available for 26 *C. glabrata* isolates. The MIC_{50} was 32 µg/ml and MIC_{90} was 64 µg/ml for fluconazole and 46.15% (n=12/26) isolates were susceptible to dose dependant fluconazole. The voriconazole MIC_{50} was 0.25 µg/ml and MIC_{90} 1 µg/ml. All *C. glabrata* isolates were susceptible to amphotericin B but MICs were not available.

Table 4: Laboratory results

	C. auris		*C. albicans*		*C. glabrata*		*C. auris vs C. albicans*	*C. auris vs C. glabrata*
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)	**p=0.014**	**p=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)	p=0.092	p=0.468
Platelet count [109/L], median (IQR)	n=43	260 (161-351)	n=42	232 (179.25-342)	n=44	209 (124.5-341.25)	p=0.782	p=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)	p=0.127	p=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)	p=0.638	p=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)	**p=0.015**	**p=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)	**p=0.002**	**p=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)	p=0.549	p=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)	p=0.175	**p=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)	p=0.827	p=0.355

Figures in **bold** indicate statistical significance.

iv. Risk factors

There was an association between the use of indwelling devices and *C. auris* infection, compared to patients with *C. albicans* and *C. glabrata* infection. Of the *C. auris* patients with indwelling devices, 18 patients had both Quinton (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 ($p<0.001$).

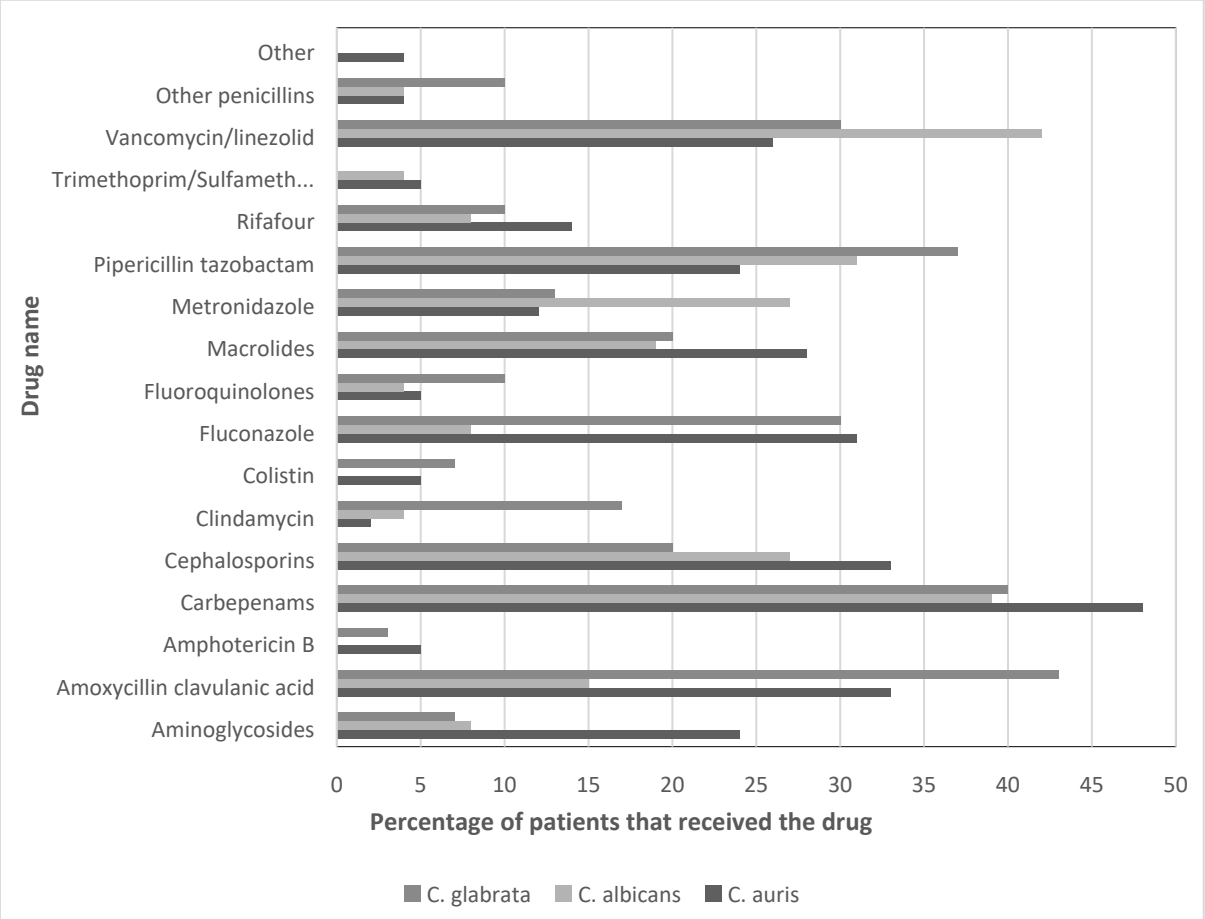

Figure 2: Individual antimicrobials and the percentage of patients that received each drug.

Of the 35 patients, with *C. auris*, who underwent a surgical procedure, 57.14% (n=20/35) had abdominal surgery, 25.71% (n=9/35) patients had thoracotomies and 14.29% (n=5/35) had craniotomies. Repeat/relook surgery was done 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. *Candida* is a gut commensal and intra-abdominal contamination may account for the positive *Candida* cultures.

During the course of their admission, 97.78% (n=44/45) of patients with *C. auris*, 57.78 % (n=26/45) of *C. albicans* and 60% (n=27/45) of *C. glabrata* patients were admitted to ICU. Of the total *C. auris* cases, 80% (n=36/45) were diagnosed during the course of ICU admission. From the two other groups, 46.67% (n=21/45) *C. albicans* and 37.78% (n=17/45) of *C. glabrata* were diagnosed in ICU.

Table 5: Risk factors for *Candida* infections.

	C. auris		***C. albicans***		***C. glabrata***		***C. auris* vs *C. albicans***	***C. auris* vs *C. glabrata***
	N	% (n)	N	% (n)	N	% (n)		
Previous hospitalization	45	8.89 (4)	45	13.33 (6)	45	26.67 (12)	p=0.502	p=**0.008**
Median number of days from		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)	**p<0.001**	**p<0.001**
Indwelling devices								
Urinary catheter	44	86.36 (38)	45	48.89 (22)	45	57.78 (26)	**p<0.001**	**p=0.007**
Central line	44	95.45 (42)	45	55.56 (25)	45	64.44 (29)	**p<0.001**	**p<0.001**
NGT	43	72.09 (31)	45	35.56 (16)	45	48.89 (22)	**p<0.001**	**p=0.030**
Post op drain	44	29.55 (13)	45	11.11 (5)	45	8.89 (4)	p=0.058	**p=0.028**
Quinton	43	41.86 (18)	45	13.33 (6)	45	11.11 (5)	**p=0.004**	**p=0.002**
A- line	43	60.47 (26)	45	26.67 (12)	45	37.78 (17)	**p=0.002**	**p=0.037**
TPN	43	51.16 (22)	45	13.33 (6)	45	26.67 (12)	**p<0.001**	**p=0.022**
HIV	45	20 (9)	45	17.78 (8)	45	18.18 (8)	p=0.788	p=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)	**p<0.001**	**p<0.001**
Immunosuppressant								
Steroid	42	38.01(16)	45	35.56 (16)	45	33.33 (15)	p=1.0	p=0.975
Other immunosuppressant	42	11.90 (5)	45	15.56 (7)	45	6.67 (3)	p=0.773	p=0.757
Organ or stem cell transplant	45	4.44 (2)	45	4.44 (2)	45	2.22 (1)	p=1.0	p=0.557
ICU admissions	45	97.78 (44)	45	57.78 (26)	45	60 (27)	**p<0.001**	**p<0.001**
Mechanical ventilation	45	82.22 (37)	45	51.11 (23)	45	57.78 (26)	**p=0.002**	**p=0.011**
Surgical procedure	45	77.78 (35)	45	66.67 (30)	45	64.44 (29)	p=0.239	p=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)	**p=0.007**	p=1.0
Diabetes	45	8.89 (4)	45	6.67 (3)	45	22.22 (10)	p=0.694	p=0.081
Chronic kidney disease	45	17.78 (8)	45	8.89 (4)	45	4.44 (2)	p=0.215	**p=0.044**

*p values in Bold text are significant

v. Treatment

Treatment data for 43 patients with *C. auris* was available. Of the total patients, 34.89% (n=15/43) were not treated. Seven of the untreated patients died between 1-12 days after a positive 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. Of the remaining two patients, both were treated with fluconazole. Appropriateness of doses were difficult to assess as the weight of patients was not routinely recorded in all files. 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 and 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 4 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.

vi. 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 (IQR1-14). Of the *C. auris* patients that died, 94.74% (n=18/19) had ICU acquired infections (as per study definition of 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.

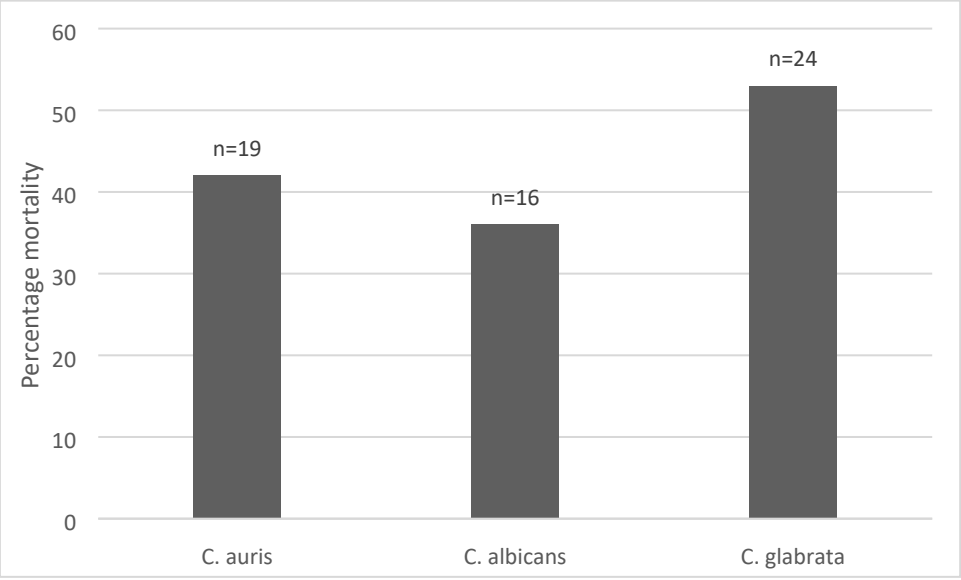

Figure 3: 30 day all-cause in-patient mortality

Odds ratios were calculated for various factors that potentially have an impact on mortality. This is shown in table 6.

Table 6: Factors associated with mortality

	Odds Ratio (95% Confidence interval)		
	C. auris	***C. albicans***	***C. glabrata***
Site of culture			
Blood	3.73 (1.06-13.12)	2.45 (0.64-9.44)	5.29 (1.44-19.45)
Urine	0.8 (0.18-3.48)	0.72 (0.18-2.94)	0.23*
Catheter tip	0.66 (0.19-2.33)	0.65 (0.11-3.96)	2.29*
Other organisms cultured	1.69 (0.5-5.68)	1.11 (0.34-3.63)	1.71 (0.51-5.74)
Risk factors			
Urinary Catheter	17.31 (3.47-86.35)	2.74 (0.81-9.31)	7.22 (1.91-27.3)
Central Line	8.87 *	2.53 (0.73-8.71)	5.78 (1.52-21.93)
NGT	1.82 (0.47-7.01)	2.44 (0.7-8.52)	3.47 (0.99-12.09)
Quinton	2.08 (0.52-8.34)	3.33 (0.46-24.05)	5.72*
A-line	0.69 (0.14-3.28)	27 (2.34-311.17)	1.63 (0.21-12.42)
TPN	1.95 (0.56-6.73)	0.5 (0.11-3.96)	1.03 (0.27-3.94)
Antibiotic exposure	4.37*	2 (0.58-6.95)	3 (0.83-10.81)
ICU admission	4.71*	3.27 (0.91-11.74)	9.1 (2.3-35.94)
Mechanical ventilation	6.25 (1.09-35.68)	5.29 (1.44-19.45)	4.65 (1.3-16.61)
Surgery	0.58 (0.13-2.58)	0.51 (0.14-1.78)	1.64 (0.48-5.62)
Treatment			
No treatment	0.57 (0.15-2.23)	0.4 (0.12-1.36)	0.43 (0.13-1.44)
Amphotericin B	0.46*	2.57 (0.21-31.71)	0.42 (0.04-4.66)
Micafungin	0.55 (0.11-2.67)	N/A	N/A
ICU acquired	7.95 (1.42-44.66)	2.2 (0.66-7.35)	3.75 (0.98-14.38)

*Haldane Anscombe correction applied.

Discussion

This study demonstrates that *C. auris* is indeed an emerging threat in South Africa. *C. auris* is a healthcare associated infection, specifically associated with ICU admissions. Units with high rates of *C. auris* infection should not use fluconazole for empiric therapy. The mortality rate in this cohort was 42%. Mortality ranges from 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 those patients was 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. This is in keeping with previous studies. However, 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, but in this study the median time was 8 days[25].

Patients were not routinely screened for *C. auris* colonization on admission. The 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. 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. Altered mental state was difficult to ascertain from the clinical notes as objective mental state, and the reasons for altered mental state, were not documented adequately for each patient.

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[35]. Median PCT in candidemia was found to be 0.7 µg/l [36], 0.99 µg/l [37] and 0.5 µg/l [38] in 3 different studies. In combination, a raised CRP with a low positive PCT may suggest an isolated fungal infection[38,39]. BDG sensitivity was 86.67% for *C. auris*. BDG can be used as a marker of fungal infections but cannot be used to distinguish between different *Candida* species[26].

Candida pneumonia is a very rare entity, and it is generally assumed that the culture represents colonization or contamination[34]. Of the *C. glabrata* patients with culture positive sputum, 75% (n=6/8) of patients were not treated and50 % (n=3/6) of these patients died. Of the patients with

C. glabrata on tracheal aspirate, 61.54% (n=8/13) were not treated and 50% (n=4/8) of these patients died. Given the number of deaths, *C. glabrata* pneumonia needs to be explored further.

The *C. auris* MIC for Amphotericin B ranged from <0.03 µg/ml to 1 µg/ml and 0.06 µg/ml to 0.12 µg/ml for micafungin. The MIC for amphotericin B is lower than other published studies[12,14,15] but the MIC for micafungin is similar to previous studies[10,11,12,14]. 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 was 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.

From the statistics above, 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 measured on admission. Immunosuppressant use, specifically glucocorticoids, was documented in many patients but was not a statistically significant risk factor for the development of *C. auris*.

Previous studies have found that surgical procedures are a risk factor for the development of *C. auris* infections, specifically abdominal surgery[25]. In this study, the number of repeat surgeries was significantly associated with *C. auris* infection.

Previous studies show that antimicrobial exposure is a risk factor for *C. auris* infection[10,11,15]. This study shows the same findings of antimicrobial exposure being statistically significant in both groups ($p<0.001$).

C. auris is currently regarded as a purely healthcare associated infection. 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. It is difficult to conclude if *C. auris* associated infection was the reason for ICU admission, or if ICU admission was the risk factor for development of *C. auris*. The number of days, from admission to ICU, to diagnosis of *C. auris* was not recorded.

The findings of this study are limited as a result of 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, instead of prioritizing the ward and age. A control group with no candidemia was not included to compare clinical findings and risk factors, thus the data provided here may be partial. 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.

Conclusion

At CMJAH, *C. auris* is a healthcare associated infection specifically associated with ICU admission and a longer duration of stay (compared to two other commonly isolated *Candida* species). Prolonged hospitalisation and prior broad-spectrum antimicrobials are associated with acquisition of the pathogen. 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. However, these may only be valuable in cases where no concomitant bacterial infection is present. Based on the outcome data presented in this study, echinocandins should become more accessible to public sector hospitals.

It is imperative that intensive infection control measures are implemented in all South African hospitals in order to prevent *C. auris* from becoming endemic. It is essential to assess the need of indwelling devices and their removal as soon possible. Most importantly, a commitment to robust antimicrobial stewardship programmes is required countrywide in order to curb resistance and development of further multidrug resistant pathogens.

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CHAPTER 3: APPENDICES

Datasheet

Data Sheet			
1. Demographics			
1.1. Age:		1.2. Gender:	Male ☐ Female ☐
1.3. Study Number			
2. Clinical Features			
2.1. Hypotension:	Yes ☐	No ☐	
2.2. Altered mental state:	Yes ☐	No ☐	
2.3. Fever:	Yes ☐	No ☐	If (2.3) is Yes, duration in days
2.4. Sepsis:	Yes ☐	No ☐	
2.5. Septic shock:	Yes ☐	No ☐	
3. Symtoms Developed			
3.1. After hospital stay? Yes ☐ No ☐		If (3.1) is Yes, length of stay (days)	
3.2. Number of days post admission that symptoms developed			
4. Laboratory Features			
4.1. Number of days after admission positive result obtained			
4.2. Organism			
4.2.1. Candida Auris	☐		
4.2.2. Candida Glabrata	☐		
4.2.3. Candida Albicans	☐		
4.3 Site of culture			
Urine ☐ Blood ☐ Tissue ☐ CSF ☐ Catheter tip ☐			
Sputum ☐ Body Fluid ☐ Other ☐			
4.4. Haemoglobin [g / dL]			
4.5. White cell count [10^9/L]			
4.6. Neutrophil count [10^9/L]			
4.7. Platelet count [10^9/L]			
4.8. Albumin [g/L]			
4.9. Creatinine [µmol/L]			
4.10. C-reactive protein [mg/L]			
4.11. Pro calcitonin ug/L			
4.12. Beta D Glucan pg/ml			
4.13. Minimum Inhibitory Concentration			
4.13.1. Fluconozole			
4.13.2. Amphotericin B			
4.13.3. Caspofungin			
4.13.4. Micafungin			
4.14. Other organisms cultured at the same time as Candida			

5. Risk Factors

5.1. Previous hospitilization? Yes ☐ No ☐

If (5.1) is Yes, Number of days from discharge to current admission ☐

5.2. Indwelling device:

5.2.1. Catheter:	Yes ☐	No ☐
5.2.2. Central line:	Yes ☐	No ☐
5.2.3. Total parenteral nutrition:	Yes ☐	No ☐
5.2.4. Nasogastric Tube (NGT):	Yes ☐	No ☐
5.2.5. Post op drain:	Yes ☐	No ☐
5.2.6. Other:	Yes ☐	No ☐

5.3. HIV? Yes ☐ No ☐ If (5.3) is Yes, CD4 count ☐

5.4. Antibiotic exposure: Yes ☐ No ☐ No. of days from first dose to positive result

5.4.1. Carbapenem	☐	5.4.4. Co-amoxyclav	☐
5.4.2. Cephalosporins	☐	5.4.5. Aminoglycosides	☐
5.4.3. Fluroquinolones	☐	5.4.6. Antifungal- azole/Ampho B	☐

5.4.7. Gram positive antibiotics eg. Vancomycin ☐

5.5. Organ or stem cell transplant	Yes ☐	No ☐			
5.6. ICU admissions	Yes ☐	No ☐			
5.7. Mechanical ventilation	Yes ☐	No ☐			
5.8. Surgery	Yes ☐	No ☐			
5.8.1. Surgical procedure	☐				
5.9. Long term care facilities	Yes ☐	No ☐			
5.10. Malignancy	Yes ☐	No ☐			
5.10.1. Solid ☐	5.10.2. Haematologic ☐				
5.11. Diabetes	Yes ☐	No ☐			
5.12. Chronic Kidney Disease	Yes ☐	No ☐			
5.13. Immunosuppressant use	Yes ☐	No ☐	Steroids ☐	Other ☐	

6. Infection control measures

6.1. Patient isolated?	Yes ☐	No ☐
6.2. Patient notified and assessed by infection controlled team?	Yes ☐	No ☐
6.3. Room disinfected after patient removal?	Yes ☐	No ☐

7. Treatment

7.1. Treatment initiated: Yes ☐ No ☐ Number of days after positive result ☐

7.1.1. Fluconozole	☐	Dose	☐	Duration	☐
7.1.2. Voriconazole	☐	Dose	☐	Duration	☐ ☐
7.1.3. Itraconazole	☐	Dose	☐	Duration	☐ ☐
7.1.4. Other Azoles	☐	Dose	☐	Duration	☐ ☐
7.1.5. Amphotericin B	☐	Dose	☐	Duration	☐
7.1.6. Echinocandin	☐	Dose	☐	Duration	☐

8. Outcome

8.1. Demised? Yes ☐ No ☐

If (9.1) is Yes: Number of days after positive result ☐

8.2. Successfully treated? Yes ☐ No ☐

8.3. Persistant fungemia? Yes ☐ No ☐

Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Amirah Parak

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180307

NAME: (Principal Investigator)	Dr Amirah Parak
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital National Health Laboratory Service
PROJECT TITLE:	Disease Profile and Outcomes of Patients with Candida auris Infections, compared to other Candida species, at a tertiary South African Hospital
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr S. Stacey and Dr V. Chibabhai
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	24/07/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

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Abstract Introduction Multidrug resistant Candida auris is a novel and emerging threat worldwide. It has been identified in Africa, however, there is not enough data available comparing C. auris to other Candida species found in Africa. Objective To compare the clinical and biochemical features, risk factors, treatment and outcome of C. auris to the most virulent Candida species (Candida albicans) and a well-known azole resistant Candida species (Candida glabrata). Method Retrospective, cross-sectional, analysis of all patients diagnosed with C. auris infection, from 1 January 2015 to 31 August 2018, at a tertiary South African Hospital. An equal number of patients with C. albicans and C. glabrata were matched for comparison. Results Forty-five cases of C. auris infection were identified. The median age was 32 years (IQR 26- 46) with 71.1% (n=32/45) being male. Median duration of hospital stay for C. auris was 64 days (IQR 39-88) and median time from admission to diagnosis was 35 days (IQR 21-53), both of which were significant compared to C. albicans and C. glabrata ($p<0.001$). Indwelling devices and previous antibiotic exposure were found to be significant risk factors. There were no C. auris isolates resistant to amphotericin B or micafungin. 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). All C. auris isolates were healthcare associated with 80% (n=36/45) acquired in ICU. ICU admission was found to be a significant risk factor. 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. Conclusion C. auris is an emerging multi drug resistant threat in South Africa. Improved access to echinocandins in the public sector is needed for the treatment of C. auris infections. In addition, implementation of improved infection prevention and control strategies are imperative to prevent this multi-drug resistant pathogen from becoming endemic in South Africa. 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 infections, especially blood stream infections[3,4]. In the past, Candida albicans was the predominant cause of infection, however, there has been a shift towards non-albicans Candida species (NAC) causing disease[5,6]. Candida auris is an emerging Candida species that causes healthcare associated infections. C. auris was first identified in 2009, from the external ear canal of a patient in Japan[7]. It has since been identified in South American countries, the United States, Europe and South Africa, amongst many other countries[8-18]. Prior to 2016, 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 Candida species followed by C. albicans. It also found that C. auris was the fourth commonest Candida causing disease[22]. Eleven percent of candidemia in South Africa was due to C. auris in 2016-2017 and 94.2% of these cases were identified in the Gauteng province[23,24]. Length of hospitalisation appears to differ between species. It was found that the average number of days between hospitalization and identification of C. auris infection was 24 days[14] and 27.5 days[15] in two different studies. The median number of days from admission to detection of C. glabrata was 3.5 days (range 0.8-13)[25]. In a previous study of 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]. Beta-D-glucan (BDG) is found to be more sensitive than blood culture for the diagnosis of deep-seated Candida infections due to C. albicans and C.

glabrata. However, minimal information is available regarding the sensitivity of BDG for diagnosis of invasive C. auris infection[26]. Known risk factors for acquisition of C. auris are found to be 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[10,11,12,14,15,23,27]. Mortality ranged 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]. A meta-analysis of 742 C. auris isolates, globally, found the resistance profile to be as follows: 44.29% fluconazole, 15.46% amphotericin B, 12.67% voriconazole, 3.48% caspofungin, 1.95% flucytosine, 1.25% anidulafungin, 1.25% micafungin[28]. However, in a study performed in India, all isolates were resistant to fluconazole and 73% were resistant to voriconazole[11]. Based on these susceptibility data, the CDC and Public Health England recommend echinocandins as first line treatment. The NICD recommends either amphotericin B or echinocandins [18,29,30]. Aim of the study Little information is available on C. auris compared to other Candida species. C. albicans is the prototypical Candida species and regarded as the most virulent. C. glabrata is a well-known azole resistant Candida species. C. auris has been found to be as virulent as C. albicans[31] as well as multidrug resistant[28]. The study will therefore compare clinical features, risk factors and outcomes of C. auris, to the most virulent species (C. albicans), as well as an azole-resistant species, namely C. glabrata. Globally, echinocandins are recommended as first line treatment but the South African public sector has minimal, if any, access to liposomal amphotericin B and echinocandins. Methods and study design Study population and study design This retrospective, cross-sectional, study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary 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 (provided they were cultured within the same admission) were counted as a single case. The corresponding number of patients with C. glabrata and C. albicans were chosen by ward, age and if possible, site of culture. It was, however, not possible to match age exactly for each patient. Therefore, patients with the closest age (within a 10-year range) were included. Microbiological methods Routine culture medium was used to culture C. auris. The Vitek 2® (bioMerieux, Marcy- L'Etoile) 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[32]. The Fungitell BDG assay (Associates of Cape Cod, Massachusetts) is used at the NHLS. Fungitell results <60 pg/ml were reported as negative, 60- 80 pg/ml as equivocal and >80 pg/ml as positive. Data collection Inpatient files were retrieved from the archives of CMJAH. Information on demographics, clinical features, laboratory investigations, risk factors, treatment and outcomes were entered into an anonymized Microsoft Excel data capture sheet. Statistical analysis Each group of organisms was analysed separately. 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). StatisticaTM (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. Odds ratios were calculated for factors associated with mortality. The Haldane-Anscombe correction was applied to the odds ratio if one of the variables was zero. Study definitions i. Healthcare associated infection- a positive Candida culture, from a sterile site, more than 48 hours after admission, associated with clinical or laboratory features of infection. ii. ICU acquired candidiasis- Culture of Candida species obtained 48 hours after ICU admission or within 48 hours of discharge from ICU. iii. Antifungal exposure- empiric or prophylactic therapy with an antifungal agent up to 30 days prior to the diagnosis of candidiasis. iv. Antibiotic exposure- empiric or prophylactic therapy with an antibiotic up to 30 days prior to the diagnosis of candidiasis. v. Outcome- determined 30 days after the diagnosis of candidiasis. vi. Persistent fungemia- culture persistently positive after 14 days of appropriate antifungal therapy and adequate source control. vii. 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. viii. Temperature spikes- An intermittent sharp rise in body temperature, with resolution to baseline. These intermittent increases in temperature lasted between 24 and 48 hours. ix. Sepsis- life threatening organ dysfunction caused by dysregulated host response to infection[33]. x. Septic shock- Sepsis with circulatory and cellular/metabolic dysfunction[33]. xi. Hypotension- systolic blood pressure < 90mmhg and diastolic blood pressure <60mmhg. Ethical considerations This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number: M180307). Permission was obtained from the NHLS for acquisition of data, Department of Internal medicine at CMJAH and the Chief executive officer of CMJAH. The protocol was also entered into the South African Department of Health National Health Research Database (Reference GP_201806_047). Results i. Overall From 1 January 2015 to 31 August 2018, C. auris isolates were identified from clinical specimens of 45 patients. Demographics are summarized in table 1 and site of culture in table 2. All C. auris infections were healthcare associated, whereas 80% (n=36/45) of both C. albicans and C. glabrata were healthcare associated. Table 1: Patient demographics and length of stay C. auris C. albicans C. glabrata C. auris vs C. albicans C. auris vs C. glabrata 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%) p=0.186 p=0.267 Total length of hospital stay (days), median (IQR) 64 (39-88) 27 (14-37) 21 (12-44) p<0.001 p<0.001 Number of days from admission to positive result, median (IQR) 35 (21-53) 8 (3-19) 8 (2-18) p<0.001 p<0.001 Figures in bold indicate statistical significance. ii. 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). Of the C. auris patients, 50 % (n=6/12) with a fever and hypotension, cultured bacteria as well. Table 2: Site of culture C. auris C. albicans C. glabrata C. auris vs C. albicans C. auris vs C. glabrata Site of culture, %(n) Sterile Blood 57.78 (26) 26.67 (12) 48.89 (22) p=0.003 p=0.398 Tissue 4.44 (2) 6.67 (3) 6.67 (3) p=0.645 p=0.645 Cerebrospinal fluid 0 0 0 N/A N/A Body fluid* 2.22 (1) 26.67 (12) 11.11 (5) p<0.001 p=0.091 Bone 2.22 (1) 2.22 (1) 0 N/A N/A Catheter tip 33.33 (15) 13.33 (6) 2.22 (1) p=0.025 p<0.001 Non sterile Urine 20 (9) 24.44 (11) 2.22 (1) p=0.612 p=0.007 Sputum 0 6.67 (3) 17.78 (8) p=0.078 p=0.003 Superficial swab 4.44 (2) 0 0 N/A N/A rectal swab 2.22 (1) 0 2.22 (1) N/A N/A tracheal aspirate 0 8.89 (4) 28.89 (13) N/A N/A Stool 0 2.22 (1) 0 N/A N/A Figures in bold indicate statistical significance. *Body fluid collected during gastro-

intestinal surgery. Page | 7 Table 3: Clinical Features C. auris C. albicans C. glabrata C. auris vs C. albicans C. auris vs C. glabrata Hypotension, 12 10 15 n (%) N=41 (29.27) N=45 (22.22) N=45 (33.33) p=0.45 p=0.68 Altered mental state, 16 14 17 n (%) N=41 (39.02) N=45 (31.11) N=43 (39.53) p=0.44 p=0.91 Fever, n (%) N=41 28 (68.29) N=45 14 (31.11) N=45 15 (33.33) p<0.001 p=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) p=0.04 p=0.1 Septic shock, 11 12 n (%) N=41 (26.83) N=45 9 (20) N=45 (26.67) p=0.45 p=0.99 Figures in bold indicate statistical significance. iii. Laboratory features C. auris was cultured from non-sterile sites in 26.66% of cases (n=12/45). From the patients who cultured C. auris from a catheter tip, 40% (n=6/15) also had positive blood cultures, confirming a catheter-related bloodstream candidemia. Of the nine patients who cultured C. auris from urine samples, eight patients had an indwelling urinary catheter and the information of the ninth patient was unknown. Candida pneumonia is a very rare entity, and it is generally assumed that the culture represents colonization or contamination[34]. However, of the C. glabrata patients with culture positive sputum, 75% (n=6/8) of patients were not treated, 50 % (n=3/6) of these patients died. Of the patients with C. glabrata on tracheal aspirate, 61.54% (n=8/13) were not treated and 50% (n=4/8) of these patients died. Given the number of deaths, C. glabrata pneumonia needs to be explored further. Table 4 summarizes the laboratory results. Very few patients had a neutrophil count measured with the total white cell count, therefore neutrophil count was not assessed. Bacteria were cultured from clinical samples 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 (Figure 1) were multidrug resistant Page | 8 Acinetobacter baumanii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus species, Serratia marcescens, Burkholderia cepacia complex, Escherichia coli, Enterococcus faecium and Enterococcus faecalis. Other Staphylococcus species Serratia marcescens Organism cultured Pseudomonas aeruginosa Klebsiella pneumoniae ESBL Klebsiella pneumoniae Escherichia coli Enterobacter species Enterococcus species Carbepenam resistant enterobacteriacae Burkholderia cepacia Acinetobacter baumanii 0 1 2 3 4 5 6 7 8 9 Number of patients C. glabrata C. albicans C. auris Figure 1: Bacteria cultured concurrently with Candida species. Only 33.33 % (n=15/45) of patients with C. auris, 31.11% C. albicans (n=14/45), 37.78% C. glabrata (n=17/45) had a BDG test performed on blood. Sensitivity of BDG was 86.67% for C. auris, 92.31% for C. albicans and 64.71% for C. glabrata. Page | 9 Table 4: Laboratory results C. auris C. albicans C. glabrata C. auris vs C. albicans C. auris vs C. glabrata 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) p=0.014 p=0.038 White cell count [109/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) p=0.092 p=0.468 Platelet count [109/L], median (IQR) n=43 260 (161-351) n=42 232 (179.25-342) n=44 209 (124.5-341.25) p=0.782 p=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) p=0.127 p=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) p=0.638 p=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) p=0.015 p=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) p=0.002 p=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) p=0.549 p=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) p=0.175 p=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) p=0.827 p=0.355 Figures in bold indicate statistical significance. Page | 10 Forty-one patients had susceptibility results available for C. auris, but only 25 patients had MIC data available. All 41 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 dose dependant to 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. iv. Risk factors There was an association between the use of indwelling devices and C. auris infection, compared to patients with C. albicans and C. glabrata infection. Of the C. auris patients with indwelling devices, 18 patients had both Quinton (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). Page | 11 Other Other penicillins Vancomycin/linezolid Trimethoprim/Sulfamethoxazole Rifafour Pipericillin tazobactam Metronidazole Drug name Macrolides Fluoroquinolones Fluconazole Colistin Clindamycin Cephalosporins Carbepenams Amphotericin B Amoxycillin clavulanic acid Aminoglycosides 0 10 20 30 40 50 60 Percentage of patients that received the drug C. glabrata C. albicans C. auris Figure 2: Individual antibiotics and the percentage of patients that received each drug. Of the 35 patients, with C. auris, who underwent a surgical procedure, 57.14% (n=20/35) had abdominal surgery, 25.71% (n=9/35) patients had thoracotomies and 14.29% (n=5/35) had craniotomies. Repeat/relook surgery was done 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). During the course of their admission, 97.78% (n=44/45) of patients with C. auris, 57.78 % (n=26/45) of C. albicans and 60% (n=27/45) of C. glabrata patients were admitted to ICU. Of the total C. auris cases, 80% (n=36/45) were diagnosed during the course of ICU admission. From the two other groups, 46.67% (n=21/45) C. albicans and 37.78% (n=17/45) of C. glabrata were diagnosed in ICU. Page | 12 Table 5: Risk factors for Candida infections. C. auris C. albicans C. glabrata C. auris vs C. C. auris vs C. albicans glabrata N % (n) N % (n) N % (n) Previous hospitalization 45 8.89 (4) 45 13.33 (6) 45 26.67 (12) p=0.502 p=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) Indwelling devices Urinary catheter 44 86.36 (38) 45 48.89 (22) 45 57.78 (26) p<0.001 p=0.007 Central line 44 95.45 (42) 45 55.56 (25) 45 64.44 (29) p<0.001 p<0.001 NGT 43 72.09 (31) 45 35.56 (16) 45 48.89 (22) p<0.001 p=0.030 Post op drain 44 29.55 (13) 45 11.11 (5) 45 8.89 (4) p=0.058 p=0.028 Quinton 43 41.86 (37) 45 13.33 (6) 45 11.11 (5) p=0.004 p=0.002 A- line 60.47 (26) 45

26.67 (12) 45 37.78 (17) p=0.002 p=0.037 TPN 43 51.16 (22) 45 13.33 (6) 45 26.67 (12) p<0.001 p=0.022 HIV 45 20 (9) 45 17.78 (8) 45 18.18 (8) p=0.788 p=0.589 CD4, median (IQR) 237 (129-379) 45 89 (29.5-333) 45 36 (10.72.5) Antibiotic exposure 43 97.67 (42) 44 59.09 (26) 45 66.67 (30) p<0.001 p<0.001 Immunosuppressant Steroid 42 38.01(16) 45 35.56 (16) 45 33.33 (15) p=1.0 p=0.975 Other immunosuppressant 42 11.90 (5) 45 15.56 (7) 45 6.67 (3) p=0.773 p=0.757 Organ or stem cell transplant 45 4.44 (2) 45 4.44 (2) 45 2.22 (1) p=1.0 p=0.557 ICU admissions 45 97.78 (44) 45 57.78 (26) 45 60 (27) p<0.001 p<0.001 Mechanical ventilation 45 82.22 (37) 45 51.11 (23) 45 57.78 (26) p=0.002 p=0.011 Surgical procedure 45 77.78 (35) 45 66.67 (30) 45 64.44 (29) p=0.239 p=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) p=0.007 p=1.0 Diabetes 45 8.89 (4) 45 6.67 (3) 45 22.22 (10) p=0.694 p=0.081 Chronic kidney disease 45 17.78 (8) 45 8.89 (4) 45 4.44 (2) p=0.215 p=0.044 *p values in Bold text are significant Page | 13 v. Treatment Treatment data for 43 patients with C. auris were available. Of the total patients, 34.89% (n=15/43) were not treated. Seven of the untreated patients died between 1-12 days after a positive result. Three of these patients had candidaemia, 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 positive result to initiation of treatment was 5 days (IQR 3.25-7). 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 escalated 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. Appropriateness of doses were difficult to assess as the weight of patients was not routinely recorded in all files. 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. 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 and 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 escalated to micafungin. The median time from positive result to commencement of treatment was 4 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. vi. 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 (IQR1-14). Of the C. auris patients that died, 94.74% (n=18/19) had ICU acquired infections. Admission to ICU was strongly associated with C. auris (p<0.001). The 30 day all-cause in patient mortality is shown in figure 3. 60 n=24 50 Percentage mortality n=19 40 n=16 30 20 10 0 C. auris C. albicans C. glabrata Figure 3: 30 day all-cause in-patient mortality Odds ratios were calculated for various factors that potentially have an impact on mortality. This is shown in table 6. Table 6: Factors associated with mortality Odds Ratio (95% Confidence interval) C.

auris C. albicans C. glabrata Site of culture Blood 3.73 (1.06-13.12) 2.45 (0.64-9.44) 5.29 (1.44-19.45) Urine 0.8 (0.18-3.48) 0.72 (0.18-2.94) 0.23* Catheter tip 0.66 (0.19-2.33) 0.65 (0.11-3.96) 2.29* Other organisms cultured 1.69 (0.5-5.68) 1.11 (0.34-3.63) 1.71 (0.51-5.74) Risk factors Urinary Catheter 17.31 (3.47-86.35) 2.74 (0.81-9.31) 7.22 (1.91-27.3) Central Line 8.87 * 2.53 (0.73-8.71) 5.78 (1.52-21.93) NGT 1.82 (0.47-7.01) 2.44 (0.7-8.52) 3.47 (0.99-12.09) Quinton 2.08 (0.52-8.34) 3.33 (0.46-24.05) 5.72* A-line 0.69 (0.14-3.28) 27 (2.34-311.17) 1.63 (0.21-12.42) TPN 1.95 (0.56-6.73) 0.5 (0.11-3.96) 1.03 (0.27-3.94) Antibiotic exposure 4.37* 2 (0.58-6.95) 3 (0.83-10.81) ICU admission 4.71* 3.27 (0.91-11.74) 9.1 (2.3-35.94) Mechanical ventilation 6.25 (1.09-35.68) 5.29 (1.44-19.45) 4.65 (1.3-16.61) Surgery 0.58 (0.13-2.58) 0.51 (0.14-1.78) 1.64 (0.48-5.62) Treatment No treatment 0.57 (0.15-2.23) 0.4 (0.12-1.36) 0.43 (0.13-1.44) Amphotericin B 0.46* 2.57 (0.21-31.71) 0.42 (0.04-4.66) Micafungin 0.55 (0.11-2.67) N/A N/A ICU acquired 7.95 (1.42-44.66) 2.2 (0.66-7.35) 3.75 (0.98-14.38) *Haldane Anscombe correction applied. Discussion This study demonstrates that C. auris is indeed an emerging threat in South Africa. C. auris is a healthcare associated infection, specifically associated with ICU admissions. Units with high rates of C. auris infection should not use fluconazole for empiric therapy. The mortality rate in this cohort was 42%. Mortality ranged from 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 those patients was 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. This is in keeping with previous studies. However, 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, but in this study the median time was 8 days[25]. Patients were not routinely screened for C. auris colonization on admission. The number of infected patients that were colonized was therefore unknown. C. auris was predominantly (84.44%, n=38/45) cultured from sterile sites which suggests infection rather than colonization. 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. Altered mental state was difficult to ascertain from the clinical notes as objective mental state, and the reasons for altered mental state, were not documented adequately for each patient. 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[35]. Median PCT in candidemia was found to be 0.7 µg/l [36], 0.99 µg/l [37] and 0.5 µg/l [38] in 3 different studies. In combination, a raised CRP with a low positive PCT may suggest an isolated fungal infection[38,39]. BDG sensitivity was 86.67% for C. auris. BDG can be used as a marker of fungal infections but cannot be used to distinguish between different Candida species[26]. The C. auris MIC for Amphotericin B ranged from <0.03 µg/ml to 1 µg/ml and 0.06 µg/ml to 0.12 µg/ml for micafungin. The MIC for amphotericin B is lower than other published Page | 17 studies[12,14,15] but the MIC for micafungin is similar to previous studies[10,11,12,14]. 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). From the statistics above, 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 measured on admission. Immunosuppressant use, specifically glucocorticoids, was documented in many patients but was not a statistically significant risk factor for the development of C. auris. Previous studies found that surgical procedures are a risk factor for the development of C. auris infections, specifically abdominal surgery[25]. In this study, the number of repeat surgeries was significantly associated with C. auris infection. 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. Candida is a gut commensal and intra-abdominal contamination may account for the positive Candida cultures. Previous studies show that antimicrobial exposure is a risk factor for C. auris infection[10 ,11, 15]. This study is in keeping (p<0.001). C. auris is currently regarded as a purely healthcare associated infection. 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. It is difficult to conclude if C. auris associated infection was the reason for ICU admission, or if ICU admission was the risk factor for development of C. auris. The number of days from admission to ICU to diagnosis of C. auris was not recorded. The findings of this study are limited as a result of 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. Page | 18 Matching of C. albicans and C. glabrata patients were performed manually and may have resulted in some bias. A control group with no candidaemia was not included to compare clinical findings and risk factors, thus the data provided here may be partial. Conclusion At CMJAH, C. auris is a healthcare associated infection specifically associated with ICU admission and a longer duration of stay (compared to two other commonly isolated Candida species). Prolonged hospitalisation and prior broad-spectrum antimicrobials are associated with acquisition of the pathogen. 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. However, these may only be valuable in cases where no concomitant bacterial infection is present. Based on the mortality data presented in this study, echinocandins should become more accessible to public sector hospitals. It is imperative that intensive infection control measures are implemented in all South African hospitals in order to prevent C. auris from becoming endemic. Most importantly, a commitment to robust antimicrobial stewardship programmes is required countrywide in order to curb resistance and development of further multidrug resistant pathogens. Page | 1 Page | 2 Page | 3 Page | 4 Page | 5 Page | 6 Page | 14 Page | 15 Page | 16 Page | 19

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I AMIRAH PARAK (Student number: 1820696) am a student registered for the degree of Master of Medicine in the academic year 2020.

I hereby declare the following:

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- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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