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Analysis of *Candida auris* fungemia at a single facility in Kenya

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ABSTRACT

Objectives: *Candida auris* emerged as a human pathogen in 2009 and has subsequently been identified around the world as a cause of invasive candidiasis. We did an analysis from a single institution in order to analyze risk factors and outcomes for *C. auris* candidemia.
Methods: Patients with candidemia were identified by the electronic medical record and reviewed for risk factors and outcome. *Candida* isolates were identified by Vitek2 as *Candida haemulonii*, but species determinations for 21 of the isolates using published molecular and proteomic methods identified all as *C. auris*.
Findings: From September 2010 to December 2016, *C. auris* accounted for 38% of 201 patients with candidemia, while *C. albicans* contributed 25%. *C. auris* patients had been hospitalized longer (mean 32 days vs. 13 days; $p < 0.001$), were more likely to have central lines preceding candidemia than *C. albicans* patients (84% vs. 54%; $p = < 0.001$) and had more commonly been treated with carbapenems (83% vs 61% for *C. albicans* [$p = 0.01$]). The crude mortality was 29%, compared to 36% for *C. albicans*.
Conclusions: These findings suggest an opportunistic pathogen that may be less virulent, but difficult to eradicate and that control efforts should focus on antimicrobial usage.

Introduction

Candidemia is currently the most commonly recognized form of invasive candidiasis and is most commonly seen in critical care settings where central vascular lines and broad-spectrum antibiotics are highly prevalent risk factors (Arendrup, 2010; Arendrup et al., 2011; Pfaller and Diekema, 2007; Pfaller et al., 2019). In series throughout the world, *Candida* species are the fourth leading cause of hospital-acquired bloodstream infection (BSI), accounting for 8 to 12% of all BSI acquired in United States hospitals (Wisplinghoff et al., 2004). In earlier series, *Candida albicans* was the dominant species, but in series reported since 2010, it has formed only 50% of the isolates (Arendrup, 2010; Cleveland et al., 2015; Guinea, 2014). In comparison, *Candida auris* is a newly identified cause of invasive candidiasis and uncommon in most series. *C. auris* is part of a complex of related species that includes *C. haemulonii*, *C. duobushaemulonii* and *C. lusitaniae* and was recognized as a human colonizer in 2009 (Satoh et al., 2009) and as a cause of invasive infection in 2011 (Lee et al., 2011). After its initial discovery in Asia, *C. auris* has been recognized as a relatively drug-resistant yeast that can cause a wide spectrum of infections, ranging from fungemia to deep-seated infections, especially in intensive care settings (Chowdhary et al., 2014; Emara et al., 2015; Lee et al., 2011; Magobo et al., 2014; Sarma et al., 2013). Recent reports have suggested a unique susceptibility profile that includes highly elevated MICs to fluconazole, and reduced susceptibility to voriconazole, echinocandins, and flucytosine (Bidaud et al., 2018; Chowdhary et al., 2014; Chowdhary et al., 2018; Chowdhary et al., 2013; Hou et al., 2019; Lee et al., 2011; Magobo et al., 2014).

Candida species are the most common agents of hospital-acquired bloodstream infection at Aga Khan University Hospital Nairobi (AKUHN) (Maina et al., 2016) and *C. auris* has been the most commonly identified species of *Candida* since 2011. As such, the institution is ideally placed to provide information on risk factors and outcomes of invasive infections caused by this pathogen. The present study provides an evaluation of the risk factors and outcomes of candidemia due to *C. auris* in comparison with that caused by *C. albicans* and other *Candida* species.

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Methods

Patient information

AKUHN is a 280-bed referral center with 50 critical care beds. Patients treated at AKUHNN who had at least one blood culture between September 2010 and December 2016 that grew *Candida* species were included in the study and medical records were reviewed for patient details and comorbidities. The main objective of this study was to assess factors that may be influencing *Candida* species, duration and mortality.

The electronic medical record (EMR) was used to identify patients with candidemia and written records were reviewed to identify details not contained in the EMR. Positive blood cultures of the same species were considered to be part of the same episode if there was less than one month between successive positive blood cultures. For patients with more than one episode, the primary episode used for analysis was the species found in the first positive culture. In order to determine whether the candidemia was likely to be the cause of death, we performed a review of the medical record during the time surrounding the candidemia to look for clinical deterioration or death within the period of two days before to a week after the death and absence of a more likely cause for the deterioration.

The BD BACTEC™ (Franklin Lakes, New Jersey), USA was used for blood cultures and the VITEK® 2 Compact (bioMérieux, Marcy-l'Étoile, France) for microbial identification and routine susceptibility testing. Vitek2 YST ID cards were used for yeast identification and Vitek2 AST YS07 for yeast susceptibility testing. The Clinical Laboratory Standards Institute (CLSI) M27-A3 breakpoints were used for interpretation (Clinical and Laboratory Standards Institute. 2008. Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd ed. Approved standard M27-A3. Clinical and Laboratory Standards Institute, Wayne, PA; Clinical and Laboratory Standards Institute M27-S4. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: 4th Informational Supplement. Wayne, PA. CLSI, 2012).

Twenty-one of the isolates identified by Vitek2 as *Candida haemulonii* were subjected to molecular identification using ribosomal intervening transcribed sequence (ITS) sequencing and pulsed field gel electrophoresis (PFGE) typing as well as MALDI-TOF (Pfaller et al., 2012). All 21 were identified as *C. auris*, and by ITS sequence comparison had 85% identity with *C. haemulonii* (sensu stricto). Thus, these isolates are referred to herein as *C. auris*. These 21 isolates were susceptibility tested by reference broth microdilution according to the CLSI guidelines (CLSI, 2008).

Ethics review

The study protocol was approved by the Ethics Committee of AKUHN with a waiver of individual consent.

Results

Appearance of C. auris

A total of 224 episodes of candidemia from September 2010 through December 2016 were seen in 201 patients (Table 1; Supplementary Table S1). The Vitek2 was first used for identification of yeasts in the laboratory in September 2010, but the first *C. auris* isolate was not seen until May 2011, suggesting the appearance of a new organism rather than recognition due to new identification method. *C. auris* rapidly became the most common *Candida* BSI isolate in 2012 followed by a general downward trend through 2016 (Figure 1). This occurred in the absence of any new or special infection control efforts or changes in antibacterial or antifungal usage. All 21 organisms evaluated by PFGE belonged to a single clade (data not shown).

Table 1
Patient characteristics, comorbidities and factors associated with *Candida* species.

	C. auris (n = 77)	*C. albicans* (n = 50)	Other (n = 74)	Bivariate Analysis P-value	
				C. auris – *C. albicans*	*C. auris* - other
Age Mean age, years (SD)	58 (20)	48 (30)	56 (25)	0.047 OR: 1.02 (1.00–1.03)	0.686
Sex Male	43 (56%)	26 (52%)	44 (60%)	0.718	0.742
Comorbid Risk Factors					
HIV	4 (5%)	3 (6.0%)	6 (8.1%)	0.598	0.612
Renal Failure before admission	30 (39%)	12 (24%)	16 (22%)	0.087	0.023 OR: 2.31 (1.13–4.75)
Diabetes	17 (22%)	12 (24%)	16 (22%)	0.632	0.831
Hypertension	17 (22%)	14 (28%)	21 (28%)	0.484	0.491
Malignancy	7 (9%)	8 (16%)	8 (11%)	0.326	0.738
Hospital Related Factors					
Renal Failure after admission	12 (25%)	9 (24%)	15 (26%)	1.000	1.000
Critical Care Unit	61 (79%)	29 (58%)	54 (73%)	0.016 OR: 2.76 (1.26–6.06)	0.446
Mechanical Ventilation	17 (22%)	10 (20%)	6 (8%)	0.895	0.034 OR: 3.17 (1.17–8.57)
Presence of CVC	65 (84%)	27 (54%)	52 (70%)	<0.001 OR: 4.61 (2.01–10.58)	0.051
Mean days with CVC (SD) (of patients who had CVC n = 144)	12 (3)	11 (5)	10 (5)	0.437	0.068
Mean days with CVC (SD) (all patients n = 201)	10 (5)	6 (6)	7 (6)	0.001 OR: 1.12 (1.05–1.19)	0.005 OR: 1.08 (1.02–1.15)
Admission to Diagnosis Duration					
Mean days (SD)	32 (26)	13 (12)	17 (27)	<0 .001 OR: 1.09 (1.04–1.13)	<0.001 OR: 1.04 (1.02–1.07)
Death in hospital	22 (29%)	18 (36%)	29 (39%)	0.493	0.183

Categorical comparisons were performed using a 2-sided Fisher's exact test. Continuous comparisons were performed using Students t-test.
CVC, central venous catheter; HIV, human immunodeficiency virus.

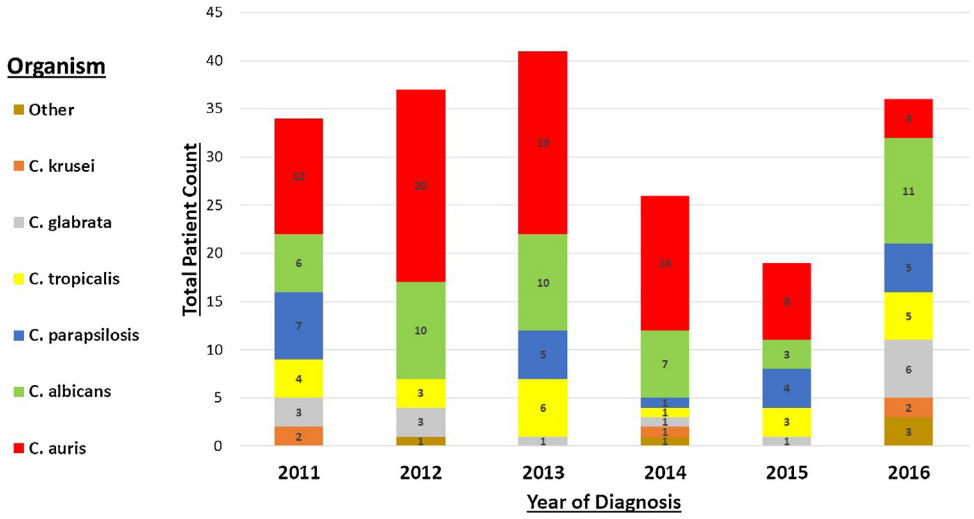

Figure 1. Yearly patterns for initial *Candida* infection from 2011 to 2016.

General characteristics of patients with candidemia

Of the 201 patients with candidemia, 131 (65%) had at least one comorbidity identified. These did not differ significantly among the different species, although there was a trend toward more chronic kidney disease in *C. auris* patients (Table 1). The most common morbidities for all candidemia patients were chronic kidney disease, hypertension and diabetes: 7% were HIV-infected, reflecting the general patient population.

The majority of patients (72%) were in a critical care unit at the time of their initial positive blood culture, with 16% requiring mechanical ventilation, 47% requiring dialysis and 72% requiring the placement of a central venous catheter (CVC). *C. auris* (79%) and other non-albicans *Candida* patients (73%) were more likely to be in a critical care unit than *C. albicans* patients (58%; p = 0.016 for the comparison of *C. auris* with *C. albicans*). *C. auris* patients were also more likely to have CVCs than *C. albicans*; a difference that persisted during a multivariate analysis (Table 3) with an odds ratio of 5.79 (p = 0.001). For the patients with CVCs, the number of days was also associated with *C. auris* in comparison with *C. albicans* as well as non-albicans Candida species (Table 1). There was also a borderline association of CVC with *C. auris* in comparison to other non-albicans species (p = 0.051), but this was not significant in the multivariate analysis.

Antimicrobial treatment prior to candidemia

Antibiotic use during the two week period prior to the candidemia was investigated to determine whether any antibiotics were more associated with *C. auris* than with other types of candidemia. During the two weeks prior to the initial blood culture that grew *Candida*, 89% of patients had received an antibiotic. *C. auris* patients had more antibiotic days during the two weeks before their first positive blood culture and had been given a greater number of antibiotics during that time, in comparison with *C. albicans* and with other *Candida* species (Table 2). The antibiotic class that was the most highly associated with *C. auris* candidemia was the carbapenems (usually meropenem) (Table 2). *C. auris*

Table 2
Antimicrobial use during two weeks prior to diagnosis.

	C. auris (n = 77)	*C. albicans* (n = 50)	Others (n = 74)	*C. auris* – *C. albicans* Comparison		*C. auris* – other Comparison	
				OR (CI)	P-value	OR (CI)	P-value
Total antibacterial use, number (%)							
Antibacterial Use	72 (94%)	44 (88%)	67 (91%)	1.96 (0.57–6.82)	0.288	1.50 (0.46–4.97)	0.503
Days of antibacterial, median (IQR)	24 (22)	14 (16)	17 (12)	1.07 (1.03–1.11)	<0.001	1.06 (1.03–1.10)	<0.001
Number of Patient days for antibiotic class							
Carbapenem	8 (4)	6 (4)	7 (4)	1.16 (1.03–1.30)	0.014	1.09 (1.00–1.20)	0.062
Glyc	8 (6)	6 (5)	6 (5)	1.08 (0.96–1.23)	0.223	1.10 (1.01–1.22)	0.046
Aminoglycoside	6 (4)	4 (5)	5 (4)	1.12 (0.94–1.39)	0.235	1.08 (0.91–1.30)	0.415
Pen/BLI	5 (4)	6 (3)	5 (5)	0.94 (0.75–1.18)	0.578	1.00 (0.87–1.15)	0.965
Linezolid	6 (4)	2 (1)	5 (4)	1.74 (1.13–3.76)	0.062	1.09 (0.90–1.33)	0.384
Number of Patients Receiving Antibiotic Class, number (%)							
Carbapenem	60 (83)	27 (61)	51 (76)	3.15 (1.32–7.50)	0.010	1.57 (0.68–3.62)	0.291
Glyc	37 (51)	14 (32)	28 (42)	2.27 (1.03–4.97)	0.041	1.47 (0.75–2.89)	0.258
Aminoglycoside	21 (29)	10 (23)	12 (18)	1.40 (0.59–3.34)	0.448	1.89 (0.84–4.22)	0.122
Pen/BLI	26 (36)	9 (21)	22 (33)	2.20 (0.92–5.28)	0.078	1.16 (0.57–2.33)	0.685
Linezolid	21 (29)	6 (14)	12 (18)	2.61 (0.96–7.09)	0.060	1.89 (0.84–4.22)	0.122
Antifungal Use Prior to Candidemia							
Amphotericin	4 (5%)	0 (0%)	0 (0%)	–	–	–	–
Echinocandin	3 (4%)	1 (2%)	3 (4%)	0.9 (0.08–11.2)	0.959	2.0 (0.32–12.24)	0.453
Azole	12 (16%)	5 (10%)	8 (11%)	0.3 (0.03–3.56)	0.370	1.6 (0.31–7.87)	0.593

Only the antibiotics where there was a significant difference between two groups in at least one comparison are shown. The complete list is shown in Supplementary Table S2.
OR, odds ratio; CI, 95% confidence interval; IQR, interquartile range; SD, standard deviation; Pen/BLI, antibiotic of the penicillin class with a beta-lactamase inhibitor; usually piperacillin/tazobactam, sometimes amoxicillin/clavulanate.

Table 3
Multivariate analysis of *C. auris* vs. *C. albicans*.

Variable	OR (95% CI)	P value
Carbapenem (Days)	1.19 (1.05–1.35)	0.007
Carbapenem (Number)	2.67 (1.06–6.75)	0.038
Critical Care Unit	3.14 (1.02–9.72)	0.047
Presence of CVC	5.79 (2.12–15.80)	0.001

Based on the Univariate analysis: age, critical care unit and presence of CVC was significant when comparing *C. auris* and *C. albicans*. These variables were used as a forward selection in a logistic regression model. Four independent associations were found.
a) After adjusting for Critical care, with an increase in one unit of carbapenem days, the odds of being a *C. auris* candidemia are 1.19.
b) After adjusting for carbapenem days, the odds of being a *C. auris* candidemia for those in Critical care unit over the odds of being a *C. auris* candidemia for those not in Critical care unit are 3.14.
c) After adjusting for presence of CVC, the odds of being a *C. auris* candidemia for those having had Carbapenem over the odds of being a *C. auris* candidemia for those not having Carbapenem are 2.67.
d) After adjusting for use of carbapenem, the odds of being a *C. auris* candidemia for those having a CVC over the odds of being a *C. auris* candidemia for those not having a CVC are 5.79.

patients were more likely to have received carbapenems before the candidemia than *C. albicans* patients and had received more days of carbapenems than *C. albicans* or other candidemia patients. The independent association was confirmed in the multivariate analysis for *C. auris* vs. *C. albicans*, both for the frequency of usage and number of days (Table 3). There were weaker associations with the use of other antibiotics including penicillin/beta-lactamase combinations (primarily piperacillin/tazobactam) and linezolid. However, these associations were not confirmed as independent associations in the multivariate analyses. *C. auris* patients were more likely to have been treated with azoles than *C. albicans* patients (OR 3.2, p = 0.052), although that included only 23% of *C. auris* patients (Supplementary Table S2).

In vitro susceptibilities of Candida *isolates*

Antifungal susceptibility testing was routinely performed for the *Candida* bloodstream isolates using the Vitek2 system and results are shown in Table 4 as an MIC range rather than susceptible vs. resistant. Although clinical breakpoints (CBPs) have not been established for *C. auris*, all isolates tested in the present study had fluconazole MICs of at least 16 mg/L and generally had voriconazole MICs at least two-fold higher than other *Candida* species. Caspofungin MIC values were generally one dilution higher than that of other species of *Candida* (MIC_{90} 0.5 mg/L versus < 0.25 mg/L, respectively) (Table 4). *C. auris* was routinely within the susceptible range for 5-flucytosine (data not shown), but this drug is not available in Kenya.

It should be noted that the Vitek2 system has not been shown to be reliable for testing *C. auris* (Kathuria et al., 2015). As such, the susceptibilities of 21 randomly selected *C. auris* isolates were also determined by the CLSI broth microdilution (BMD) method (see methods), which is generally considered to be the gold standard (Table 5). All isolates were susceptible to amphotericin (MIC, ≤1 mg/L) and caspofungin (MIC, ≤0.25 mg/L) and highly resistant (MIC ≥ 128 mg/L) to fluconazole. There was no evidence of a paradoxical growth effect (Bidaud et al., 2018) with caspofungin. Similar to fluconazole, voriconazole MIC values were elevated with 17/21 (81%) isolates tested by BMD showing MIC values at or above the resistant breakpoint of ≥1 mg/L established for *C. albicans* (CLSI, 2017).

There were 18 *C. auris* patients with documented candidemia of 14 days or longer, despite the lack of routine followup cultures in many patients, demonstrating the ability of this organism to cause prolonged candidemia. For these patients, we compared the MICs of the isolates to determine whether there was evidence for acquisition of in vitro resistance in these patients with prolonged candidemia. All Vitek2 susceptibility patterns of *C. auris* isolates from these patients are shown in Supplementary Table S4. There was frequently a difference in susceptibility of up to 4-fold, but no clear trend of increasing MIC with later isolates. Thus, there is not a clear pattern of increasing resistance over time for the agents tested.

Outcome of patients with candidemia

The mortality rate for *C. auris* patients trended toward being lower than seen for other *Candida* species, although not statistically significant (29% vs. 36% for *C. albicans* and 39% for other *Candida* species). Since the *C. auris* patients tended to be older and had been hospitalized longer before the candidemia, we determined how often early mortality resulted and whether it was likely to be related to their candidemia. There was a longer duration from the initial positive blood culture for patients who died with *C. auris* than with *C. albicans* (Supplementary Figure S1). Of the 28 patients with candidemia who died within a week of their initial blood culture, records from 25 were available to review for the likely cause of death. We examined the records to determine the likelihood that the candidemia made a significant contribution to their deaths. The candidemia was a likely contributor to the deaths for only three patients (two *C. albicans* and one *C. glabrata*) (see Supplementary Table S5).

Discussion

C. auris emerged as a cause of candidemia in May 2011 and by the following year, had become the most common species. While it is possible that earlier cases had been present in our institution, it is notable that for the first eight months of using the current identification system, there were no cases suggestive of *C. auris*. In the absence of any specific interventions, the actual number and the percentage of cases subsequently decreased over time so that in 2016, there were five cases comprising 14% of the total candidemia cases, down from a peak of 59% in 2012.

Risk factors for candidemia that have been identified in non-neutropenic hospitalized patients include critical care treatment,

Table 4
Candida susceptibilities determined by Vitek2.

	Caspofungin				Fluconazole					Voriconazole			
MIC (mg/L)	n	≤0.25	0.5	1	n	≤1	2–8	16–32	≥64	n	≤0.5	1	≥2
C. auris (n = 72)	34	20	14	0	72	0	0	18	54	72	10	47	5
C. albicans (n = 41)	23	22	1	1	41	37	21	0	2	41	38	2	1
C. parapsilosis (n = 14)	10	1	3	6	14	7	1	1	5	14	9	2	3
C. tropicalis (n = 17)	11	11	0	0	17	16	1	0	0	17	17	0	0
C. glabrata (n = 15)	10	10	0	0	15	0	14	0	1	15	14	1	3

The number of isolates at each MIC value are shown. The MICs as determined by Vitek2 includes only the first isolate in patients with susceptibilities done for more than one isolate. The number of isolates at each MIC range are noted without inferred susceptibility or resistance.

Table 5
C. auris susceptibilities determined by broth microdilution (mg/L).

	Amphotericin	Caspofungin				Fluconazole		Voriconazole		
MIC (mg/L)	1	0.03	0.06	0.12	0.25	128	>128	0.5	1	2
C. auris (n = 21)	21	1	1	6	8	6	15	4	10	7

diabetes, renal failure, vascular lines and broad spectrum antibiotics (Adams et al., 2018; Chow et al., 2018; Lockhart et al., 2017). Thus, it is notable in the current study, some of these risk factors were much more common in *C. auris* patients than in *C. albicans* patients. Notably, a CVC was present (fulfilling NHSN criteria for CLABSI) in 84% of *C. auris* patients and only 54% of *C. albicans* patients. The use of broad spectrum antibiotics was also notable, since broad spectrum antibiotics, particularly carbapenems, have been documented as risk factors for *C. albicans* candidemia. In the current series, carbapenems were used more frequently (83% vs. 61%) and for more days (8 vs. 6) for *C. auris* than for *C. albicans* patients.

The largest study of the clinical characteristics of patients with *C. auris* fungemia included 74 patients with *C. auris* candidemia from 19 ICUs in India, representing 5.3% of the *Candida* isolates (Rudramurthy et al., 2017). They found that *C. auris* was associated with longer ICU stay, pre-existing respiratory illness, antifungal exposure and low APACHE II scores. They did not find an association with presence of a CVC, but *C. auris* was associated with longer duration of central venous catheterization. Exposure to antibacterial agents was not reported in the India-based study.

The 30-day mortality of 41.9% and an estimated 27% attributable mortality was higher than that of other *Candida* species (Rudramurthy et al., 2017). In comparison, a study that included 41 *C. auris* patients from multiple continents with clinical outcome data reported a crude mortality rate of 59% (Lockhart et al., 2017). In contrast, the in-hospital mortality in the current series was 29%, which was actually lower than for other *Candida* species, even though they were older and had been hospitalized longer. A review of the records for patients who died within one week of their initial documented candidemia revealed little evidence for a substantial contribution of *C. auris* to their mortality.

The antifungal susceptibilities for *C. auris* isolates in the current series were more resistant to antifungal agents than other species already known to have reduced susceptibility to antifungal agents. For example, 93% of *C. glabrata* isolates had a voriconazole MIC $\leq$ 0.5 mg/L, but only 14% of *C. auris* had that level of susceptibility when tested by the Vitek2 system. The *C. auris* isolates were susceptible to echinocandins (caspofungin) by Vitek2 testing, but the MICs were higher than for other isolates. For example, 42% of *C. auris* isolates had caspofungin MICs $\geq$ 0.5 mg/L, a level that was rare for species other than *C. parapsilosis*. In contrast to the Vitek2 results, the microdilution MICs for caspofungin were lower, MICs 0.12 or 0.25 mg/L for most isolates. All 21 isolates that were tested by microdilution for amphotericin had MICs of 1 mg/L, which is within the susceptible range. It must be recognized that Vitek2 results for *C. auris* have been reported to be less reliable when compared to that of BMD or Etest (Kathuria et al., 2015) and this should be considered to be a limitation of this data.

These results are similar to the susceptibility patterns for *C. auris* from the Indian ICU study (Rudramurthy et al., 2017), in which the MIC50 for amphotericin was 1 mg/L and most voriconazole MICs were 0.5 or 1 mg/L. However, most of their caspofungin MICs ranged from 0.25 to 2 mg/L; similar to our Vitek2 results but higher than our BMD results. A study of 51 isolates from New York also demonstrated similar MICs with voriconazole ranging from 0.5 to 4 mg/L (MIC_{50} 2 mg/L), caspofungin 0.03 to 0.25 mg/L (MIC_{50} 0.06 mg/L), and amphotericin 0.5 to 4 mg/L (MIC_{50} 1.5 mg/L). All series have shown a high level of resistance to fluconazole. A study that included 54 *C. auris* isolates and included 25 patients with candidemia also demonstrated similar susceptibility patterns with voriconazole, caspofungin and amphotericin MIC_{50}s of 2, 0.25 and 1 mg/L, respectively (Lockhart et al., 2017).

The prolonged candidemia in a significant portion of patients despite the removal of CVCs in most cases as well as treatment with agents that have in vitro activity raises the question of how the organism persists in the intravascular space of the patient. This discrepancy between in vitro activity and clinical nonresponse suggests that biologic reasons for the lack of treatment response should be explored, considering host and organism factors. One hypothesis is that the persistence is due to intravascular infection (e.g. central vein suppurative phlebitis), perhaps through biofilm production. A recent study has demonstrated the production of biofilm by *C. auris*, although less robust than seen for *C. albicans* (Larkin et al., 2017). Further clinical data are required to determine the best treatment approaches for *C. auris*, especially in view of the prolonged candidemia that is frequently seen despite CVC removal and treatment with agents that are active in vitro.

In summary, this is an organism with a course that is typically indolent, but has the ability to cause prolonged fungemia and is of particular concern because of its reduced susceptibility to antifungal agents. It is likely that the most effective preventive measure will consist of reduced exposure of patients to antibiotics, particularly the carbapenems.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

None of the authors has a conflict of interest to report.

Roles of the authors

Rodney D. Adam: Coordinated project; data collection and analysis, writing.

Gunturu Revathi: Supervised microbiology work; data analysis, writing.

Nancy Okinda: Data collection and analysis.

Melanie Fontaine: Data collection and analysis.

Jasmit Shah: Data analysis.

Elizabeth Kagotho: Data collection and analysis.

Mariana Castanheira: Candida identification and susceptibility testing.

Michael A. Pfaller: Candida identification and susceptibility testing, writing.

Daniel Maina: Data collection and analysis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.06.001.

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