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EVALUATION OF SUSCEPTIBILITY PATTERNS OF COMMONLY USED ANTIFUNGAL MEDICATIONS AGAINST *CANDIDA AURIS*.AT ROBERT KAIRUKI HOSPITAL, TANZANIA

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EVALUATION OF SUSCEPTIBILITY PATTERNS OF COMMONLY USED ANTIFUNGAL MEDICATIONS AGAINST *CANDIDA AURIS*.AT ROBERT KAIRUKI HOSPITAL, TANZANIA

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ABSTRACT

Background: Antifungal resistance in *Candida auris* raises the morbidity and mortality rates among immunosuppressed patients globally. Information regarding antimicrobial susceptibility testing trends of *Candida auris* is scarce in local contexts. Gaining insight into the antifungal susceptibility profile of *Candida auris* is essential for its management and treatment. This study evaluated the antifungal susceptibility testing results of *Candida auris* against fluconazole, amphotericin, ketoconazole, and caspofungin.

Methods: A total of eleven samples of *Candida auris*, confirmed through both clinical and laboratory methods according to standard procedures, were analyzed for their antifungal susceptibility patterns against fluconazole, amphotericin, ketoconazole, and caspofungin at Robert Kairuki Hospital in the Dar es Salaam region of Tanzania. The evaluation of antifungal susceptibility for the *Candida auris* strains was conducted following the guidelines outlined in the Clinical and Laboratory Standards Institute (CLSI) document M27-A3.

Results: *Candida auris* isolates showed sensitive or full resistance to the tested antifungals. The rates of resistance in *Candida auris* against fluconazole, amphotericin, ketoconazole, and caspofungin were 76%, 50%, 23%, and 5%, respectively. Caspofungin was the drug that showed the highest susceptibility among all antifungals tested. `

Conclusions: Antifungal resistance of *Candida auris* to commonly prescribed antifungals such as fluconazole was alarmingly high while very low resistance rate was observed against amphotericin, caspofungin and ketoconazole.

Recommendation: The study recommends the need for comprehensive national control programs to combat antifungal resistance. Also, method-specific resistance breakpoints should be devised for accurate antifungal susceptibility testing (AST) of clinical *Candida auris* isolates for proper patient management.

Keywords: antifungal; *Candida auris*; antimicrobial resistance, antifungal susceptibility, susceptibility, clinical breakpoint.

INTRODUCTION:

On a global scale, the occurrence and rates of fungal infections have become a major concern for public health, affecting millions of people[1]. It is estimated that annually over 6.55 million people suffer from fungal diseases, leading to more than 2.55 million death [1, 2]. Compared with the importance given to fungal infections in humans, fungal diseases are relatively neglected, even if they are a source of up to 80% of human skin problems in rural areas and 20% of infections in urban areas [3]. The threat posed by *Candida auris* increases in the current COVID-19 epidemic as the number of hospitalized patients rises, providing a vulnerable environment for nosocomial infections [3, 4,5]. A recent investigation found that the mortality rate for *Candida auris* infections associated with coronavirus is 67.85%[5]. In 2016, global health organizations such as the Centers for Disease Control and Prevention (CDC) issued warnings that *Candida auris* is leading to ongoing colonization and serious infections in hospitalized individuals, requiring strict vigilance against cases [3, 4, 5]. The CDC has classified *Candida auris* as an urgent threat to human health because of its clinical consequences, economic burden, high ability to spread, absence of effective antifungal therapies, and anticipated rise in new infections in the coming decade [6]. Recently, the World Health Organization released a Fungal Pathogens Priority List that ranked *Candida auris* as the second most critical pathogen [7]. This ranking is attributed to its global emergence, continuous transmission in and between hospitals, ability to colonize patients and non-living surfaces, high mortality rates, difficulties in diagnosis, high outbreak potential, resistance to heat, partial ineffectiveness against commonly used disinfectants, and most importantly, both intrinsic and acquired resistance to antifungal therapies [8].

Antimicrobial Resistance (AMR) is a phenomenon documented by the World Health Organization (WHO) as one of the ten greatest global threats to public health facing humanity today [8]. AMR is associated with considerable health challenges and economic costs [9, 10]. The World Bank estimates that the financial repercussions of AMR could soar to USD 3.4 trillion annually if not addressed [11]. Recent instances of systemic fungal infections, particularly among immunocompromised individuals, have arisen due to the multidrug-resistant strain of *Candida auris* [12, 13, 14, 15]. *Candida auris* is characterized for being a critical pathogen worldwide that has resistance to virtually all antifungals commonly used in the treatment of invasive fungal infections [16, 17, 18]. The increase in the prevalence of multidrug-resistant *Candida auris* to different groups of antifungals is a cause for alarm, especially considering that there are few treatment options nowadays [13, 14, 19]. Moreover, it has been reported that *Candida auris* can quickly develop resistance to all three primary classes of antifungal medications, making infections difficult to treat [19, 20]. As a result, treatment options for *Candida auris* infections are restricted since many isolates exhibit resistance to various drugs [21, 22]. This notorious yeast pathogen has spread globally and has recently been declared as an urgent antimicrobial resistance threat by the CDC and placed in the critical group of the fungal priority pathogen list [1, 23, 24]. There is

currently a lack of detailed systematic acquisition data regarding the antifungal susceptibility profile of *Candida auris in* Tanzania. Assessing the susceptibility of *Candida auris* is crucial for effective management, directing suitable antifungal treatments, improving patient outcomes, and preventing the emergence of drug resistance. Consequently, this study intends to assess the susceptibility patterns of commonly used antifungal medications against *Candida auris*.

MATERIALS AND METHODS

The present study was conducted at Robert Kairuki Hospital, Tanzania.

Sample collection and handling

Samples of *Candida auris* from the Robert Kairuki microbial bank were collected in a sterile fashion by a physician and subsequently forwarded to the microbiology laboratory. Thereafter, the identification of *Candida auris* was conducted using the standard protocols including cultural and biochemical methods as proposed in various studies [25,26]. The isolates confirmed as *Candida auris* were stored at -80°C for testing their antimicrobial susceptibility.

Antifungal susceptibility test

The antifungal susceptibility testing was carried out using the concentrations of antifungal disks as suggested elsewhere [27]. The concentrations of antifungal disks used in the present study included fluconazole (30 μg), amphotericin (50 μg), ketoconazole (10 μg) and caspofungin (30 μg). Susceptibility testing for anti-fungal drugs on *Candida auris* was conducted using broth microdilution protocols for antifungal susceptibility testing (AST). Both Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) documented that, microdilution-based antifungal susceptibility testing (AST) protocols are the methods of choice for *Candida auris* [28,29]. The strip was placed in a Saboraud Dextrose Agar (SDA) that had been inoculated with a suspension of pure colonies of the *Candida auris* isolated at a 0.5 McFarland concentration. Following this, the agar plates were incubated for 24 hours at a temperature of 37°C. After the incubation period, the observed zones of inhibition were measured with a calibrated ruler to the nearest millimeter and classified as susceptible (S) or resistant (R) based on the standard guidelines provided by the Clinical and Laboratory Standards Institute [30]. Since there are no specific susceptibility breakpoints for *Candida auris* therefore, breakpoints commonly used are defined based on those established for closely related *Candida species* as documented in previously study [6].

Quality Control

In line with the guidelines set by the manufacturer, all media preparations were conducted in the Microbiology Laboratory of Robert Kairuki Hospital. All prepared culture media (plates and tubes) were checked for sterility and performance before used in identification of the *Candida auris*. During the pre-analytical, analytical, and post-analytical phases of quality assurance, all materials, equipment, and procedures were rigorously monitored. Positive controls included standard fungi and negative

control plates were included for quality control in accordance with the standard operating protocols recommended by researchers [28]. The positive and negative controls were employed to validate the quality of the isolation and identification results and to avoid the possibility of cross-contamination. Quality control involved the use of standard yeast strains that corresponded to the *Candida auris* isolate, in accordance with the standard operating protocols recommended in previously study [28].

Ethics Approach

Permission was requested from the appropriate authorities of Robert Kairuki hospital to conduct the study at their facilities. Furthermore, all study methods were carried out in accordance with declaration of Robert Kairuki Hospital guidelines and other relevant guidelines. Additionally, the study's confidentiality of data was maintained.

Statistical analysis

Descriptive analysis was performed by Microsoft excel programme version 10 for computing the percentages of susceptibility among antifungals. Resistance percentage occurrence for each isolate was used to summarize the result and presented using tables and figures.

Results

The rates of antifungal resistance in *Candida auris* isolates were notably high for fluconazole at 90.9% (10/11), followed by amphotericin at 27.3% (3/11), ketoconazole at 18% (2/11), and lastly caspofungin at 0% (0/11) (Figure 1). On the other hand, the susceptibility rates of *Candida auris* isolates were highest for caspofungin at 100% (11/11), followed by ketoconazole at 81.8% (9/11), amphotericin at 72.7% (8/11), and finally fluconazole at 0% (0/11) (Figure 1). The findings from this study demonstrated that the susceptibility of *Candida auris* to the fluconazole antifungal was 9.1% (1 out of 11), with 90.9% (10 out of 11) classified as resistant (see Table 1). Moreover, the current research showed that the *Candida auris* isolates were susceptible to amphotericin, with 72.7% (8 out of 11) susceptible and 27.3% (3 out of 11) resistant (Table 1).

Additionally, the findings revealed that the *Candida auris* isolate exhibited a susceptibility rate of 81.8% (9/11) to the ketoconazole antifungal, with 18.2% (2/11) being classified as resistant (Table 1). Furthermore, this study demonstrated that the caspofungin antifungal had a 100% susceptibility rate (11/11) for the *Candida auris* isolate, with 0% (0/11) being noted as resistant (Table 1).

Table 1:

Interpretative breakpoints of antifungal drugs

Antifungal drugs	**Susceptibility of isolate**		**Interpretation of diameter of zone of inhibition (mm) based on recommended standards [6]**	
	Susceptible%	**Resistant %**	**Susceptible %**	**Resistant %**

Fluconazole	1(9.1%)	10(90.9%)	≥39	≤29
Amphotericin B	8(72.7%)	3(27.3%)	≥15	≤12
Ketoconazole	9(81.8%)	2(18.2%)	≥32	≤20
Caspofungin	11(100%)	0(0%)	≥12	≤12

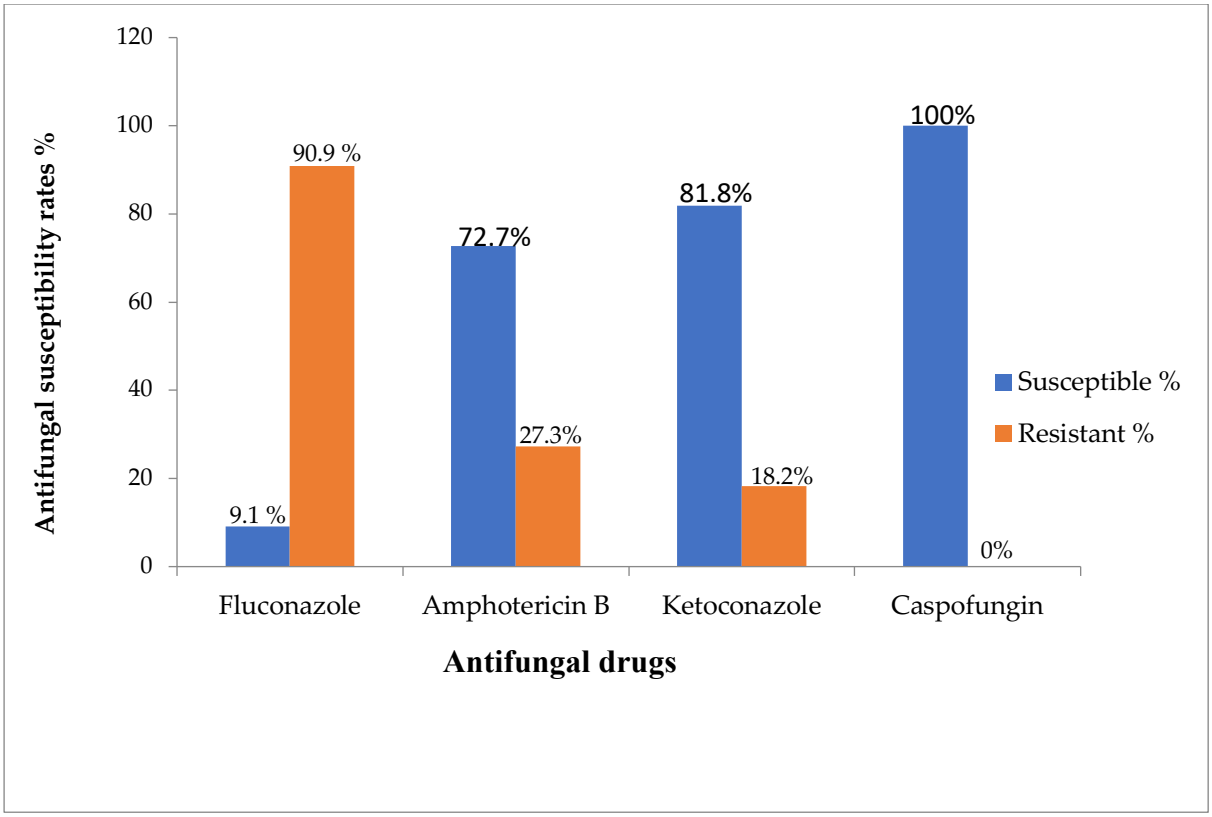

Figure 1*. Antifungal Susceptibility rate*

DISCUSSION

The present study evaluated susceptibility patterns of *Candida auris* isolate to commonly used antifungals using standard method. Antimicrobial susceptibility testing patterns of *Candida auris* isolates is as shown in Table 1 and Figure 1

The resistance rates of *Candida auris* isolates to fluconazole were notably high at 90.9% (10/11), followed by amphotericin at 27.3% (3/11), ketoconazole at 18.2% (2/11), and caspofungin showed no resistance at 0% (0/11) (Figure 1). Differences in antifungal usage may account for the varying resistance rates observed in the present study, as supported by findings in several other studies [31, 32, 33].

In this study, a high resistance rate of 91.9% alongside a low sensitivity rate of 9.1% was recorded for *Candida auris* isolates to the fluconazole antifungal, as illustrated in Figure 1. The findings presented here are lower than the 99.8% resistance reported in

the United States and the 95% in India [34]. On the other hand, this value is higher than the 90% documented in South Africa and 47% documented in a European hospital [34, 35, 36]. There are many possibilities which might explain this resistance. One explanation might be caused by prolonged and misuse of fluconazole antifungal in treatment of *Candida auris*. Frequently use, misuse, incomplete description of treatment and longer treatment *Candida auris* using fluconazole may lead to the development of resistance in these pathogenic yeasts, reducing the effectiveness of the drug. The findings of this study are in line with other authors who highlighted the consequence of misuse, overuse, and incomplete description of treatment of the aforementioned pathogen in development of antifungal resistance to fluconazole [34]. Other possible explanation for the present observation may be linked to the accumulation of mutations in chromosomal genes at three distinct sites (Y132F, K143R, and F126L or VF125AL). These mutations may disrupt the normal function of fluconazole by affecting its binding to the active sites of other enzymes (Erg6p, Erg25p, Erg26p, Erg27p, and Erg3p) within the pathway. Consequently, these mutations may diminish fluconazole binding at the active site, ultimately resulting in therapeutic failure. This observation aligns with previous research, which indicated that mutations occurring within *Candida auris* significantly contribute to the antimicrobial resistance of *Candida auris* isolates to fluconazole antifungal [37, 38]. Additionally, various studies revealed that DNA sequencing data indicated the existence of fluconazole resistance-conferring mutations in ERG11 across all *Candida* isolates [39, 40]. Nevertheless, this finding might be attributed to the overexpression of drug efflux pumps, such as ABC and MFS transporters, by *Candida auris*, which effectively expel fluconazole from the cell, reducing its intracellular concentration and diminishing its antifungal efficacy. This result is not a new scenario since various studies have highlighted the role of overexpressed drug efflux pumps in the development of resistance of *Candida auris* to fluconazole [38, 40].

The results of the current study indicate a low resistance rate of 27.3% combined with a high sensitivity rate of 72.7% for *Candida auris* isolates to the amphotericin antifungal (Figure 1). This finding exceeds the 5.5% resistance reported in South Africa [34], the 15.7% documented in South Korea [5], 24.1% , and the 25.6% also reported in united state [41], as well as the 8% recorded in India [20, 42]. In contrast, the present study reported lower results compared to the 83% found in Israel, 39% in Pakistan [20, 42], 50% in the New York-New Jersey area [34], 30% in the U.S. [34], 23% in Kuwait [43], and 30% in the U.S [34]. A possible reason for the observed resistance might be mutations occurring in the ERG genes, especially ERG2, ERG3, ERG6, and ERG11, which play a role in the biosynthesis of ergosterol. Amphotericin B displays antifungal properties by binding directly to the main fungal membrane sterol, ergosterol, which results in the creation of pores in the cell membrane and/or the sequestration of ergosterols (sterol sponging). As a result, mutations in the previously mentioned gene that impact protein function can either decrease or completely eliminate ergosterol

in the fungal cell membrane, leading to resistance against amphotericin B, as shown in various studies [22, 34, 44]. Sanger sequencing and whole genome sequencing (WGS) findings revealed that *Candida auris* exhibits resistance to the amphotericin antifungal due to mutations occurring in the ERG6 gene [22]. Additionally, the current findings may stem from the overexpression of drug efflux pumps. The increased activity of these pumps facilitates the expulsion of the antifungal agent from within the cell. Moreover, various genes can contribute to the synthesis of enzymes that break down antifungals, reducing their time of intracellular effectiveness and ultimately diminishing their therapeutic impact [45]. Nevertheless, the present observation could be caused by alteration in the fungal membrane, with changes in the amounts of sphingolipids and a reduction in ergosterol. The latter may still have its affinity reduced to amphotericin by altering the ERG3 gene, which leads to the formation of sterols with lower binding affinity for amphotericin B as previously documented in various studies [22, 45].

In this study, a low resistance rate of 18.2% was observed alongside a high sensitivity rate of 81.8% for the *Candida auris* isolate to the ketoconazole antifungal (Figure 1). The resistance rate identified in this study surpasses the 0% reported in India [46], the 7.3% resistance noted in Ethiopia [47], and the 10.3% documented in Yemen [27]. In contrast, this finding is lower than 43.7% reported in northwestern Ethiopia [49]. There are many possibilities which might explain this resistance. One possible explanation could be attributed to mutations in genes such as ERG11, which codes for the sterol-demethylase enzyme. This mechanism enables the fungus to circumvent the effects of the drug by modifying ergosterol biosynthesis, decreasing drug uptake, or enhancing drug expulsion, ultimately resulting in decreased susceptibility to ketoconazole. This finding is consistent with the previously researches which documented that, mutations in these specific regions led to the resistance observed in *Candida auris* isolates [39, 50]. Other possible explanation for this observation may be the overproduction of efflux pumps, such as CDR1, CDR2, and MDR1, which can expel the ketoconazole drug from the fungal cell, leading to a decrease in its intracellular concentration. Consequently, this may impair the drug's therapeutic effectiveness, as reported elsewhere [39]. Nonetheless, the current observation could be attributed to the buildup of sterols that are imported from the surrounding environment, which interrupts the therapeutic effectiveness of ketoconazole against the *Candida auris* isolate. This result is not a new scenario, as previous studies have documented the influence of sterol accumulation in diminishing the therapeutic efficacy of ketoconazole [51].

In the present study none (0%) of the *Candida auris* isolate was resistant to caspofungin antifungal (Figure 1).The resistance rate observed in the present study was lower than resistance rates of 2% and 7% reported in Pakistan and India [27, 47] as well as 5% in the U.S [20, 52] and less than 2% in India, and 0.25% in South Africa [34]. Conversely, the results from the present study align with the 0% resistance rate reported in the previous study

[5]. Caspofungin is more sensitive than other assessed antifungal possibly because it is not frequently given. Therefore, the less a drug is used, the less likely it is to develop resistance to it as previously documented [49].

Limitation

It was challenging to compare studies because no research has been done in Tanzania

Conclusions and Recommendations

High resistant rate of *Candida auris* to fluconazole antifungal is demonstrated in the present study. Therefore, the ban on the use of this antifungal for the treatment of *Candida auris* infections should be done. Very low/ no resistance was observed against amphotericin, ketoconazole and caspofungin antifungal. Therefore, a dual treatment regimen with amphotericin, ketoconazole and caspofungin can still be recommended as the first-line therapy for *Candida auris* in Tanzania. The present findings strongly suggest that method-specific resistance breakpoints should be devised for accurate AST of clinical *Candida auris* isolates for proper patient *man*agement. Furthermore, the findings of this study emphasize the importance of researching and developing new treatment strategies and antifungal drugs to effectively treat and control invasive fungal infections brought on by emerging fungal pathogens like *Candida auris*.

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Author contribution

Author conceptualized the research idea, acquired funding and contributed to the manuscript writing (review and editing).

Conflict of interest

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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