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Vulvovaginal Candidiasis Among Pregnant Women Attending a Tertiary Care Centre and Their Antifungal Susceptibility and Biofilm Formation

Dr. Priya Maheshwari[1], Dr. Pallav Mundra[2], Dr. Manish Purohit[3], Dr. Anju Mahor[4], Dr. Ranjana Patil[5]

[1] Resident, Department of Microbiology, MGM Medical College, Indore (M.P.)
[2] Senior Resident, Department of Clinical Hematology, MGM Medical College, Indore (M.P.)
[3] Head of the Department, Department of Microbiology, MGM Medical College, Indore (M.P.)
[4] Assistant Professor, Department of Microbiology, MGM, Medical College, Indore (M.P.)
[5] Associate Professor, Department of Obst. & Gynecology, MGM, Medical College, Indore (M.P.)

Corresponding Author:

Dr. Pallav Mundra
Senior Resident, Department of Clinical Hematology, MGM Medical College, Indore (M.P.)

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ABSTRACT

Background -In vulvovaginal candidiasis (VVC), women are affected especially in pregnancy. Hormonal and immunological alterations are the determinants of its prevalence and pathogenesis. Causative agents have been known to be Candida species, both with and without albinism. The rising resistance of antifungal agents such as fluconazole complicates the management of VVC in pregnant women. Methods: Cross-sectional study Maharaja Tukojirao Hospital, Indore, conducted the study between October 2023 and September 2024. Clinically presenting pregnant women with vaginal swabs of the vulva and vagina were enrolled. Detection The samples were subjected to direct microscopic observation, culture with fungi, identification of the species, antifungal susceptibility testing and biofilm. Results: The most frequently isolated Candida species was the 51.67% of Candida albicans and then Candida tropicalis 28.33%. A large percentage of isolates were resistant to fluconazole and biofilm production was strongly associated with resistance. The paper also pointed out that women living in urban areas, the unemployed, and those with co-morbidities such as diabetes and anemia were more likely to be infected. Conclusion: The study shows useful information on the prevalence, species distribution and patterns of antifungal resistance of VVC in pregnant women. The correlation of biofilm production and antifungal resistance, in particular, to fluconazole highlights the importance of more specific treatment approaches.

Keywords*: Candida species, Antifungal resistance, Fluconazole, Voriconazole, Biofilm formation.*

INTRODUCTION

Vulvovaginal candidiasis (VVC) represents one of the most prevalent gynecological conditions affecting women of reproductive age worldwide, with approximately 75% of women experiencing at least one episode during their lifetime.[1] Among pregnant women, this condition assumes particular clinical significance due to its increased prevalence, altered pathophysiology, and potential implications for maternal and fetal health [2,3]. The prevalence of vulvovaginal candidiasis during pregnancy varies substantially across different geographical regions, ranging from 17% to 90%, with higher rates consistently reported in developing countries[4,5].

The pathogenesis of VVC during pregnancy is multifactorial and closely linked to the physiological and hormonal changes that occur throughout gestation. Elevated levels of estrogen and progesterone during pregnancy lead to increased vaginal glycogen content, which serves as a nutrient source for Candida species [6,7]. Additionally, pregnancy-associated immunological alterations, including decreased cell-mediated immunity and changes in vaginal pH, create a favorable

environment for fungal colonization and subsequent infection [8]. These factors contribute to the observed increase in Candida colonization rates from approximately 20% in non-pregnant women to 30% during pregnancy, with the highest prevalence noted in the third trimester[9,10].

The clinical presentation of VVC in pregnancy typically includes intense vulvar pruritus, dysuria, vulvar erythema, and characteristic thick, white, cottage cheese-like vaginal discharge[11,12].However, asymptomatic colonization is also common during pregnancy, occurring in up to 30% of cases, which poses challenges for diagnosis and management [13]. The distinction between symptomatic infection and asymptomatic colonization is crucial, as treatment approaches differ significantly between these two clinical scenarios[14].

Candida albicans has traditionally been recognized as the predominant causative organism, accounting for 85-90% of VVC cases in the general population[15,16].However, recent epidemiological studies have demonstrated an increasing prevalence of non-albicans Candida (NAC) species, including *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*, particularly in certain geographic regions and among specific patient populations[17,18].This shift in species distribution has significant implications for antifungal susceptibility patterns and treatment outcomes, as NAC species often exhibit intrinsic or acquired resistance to commonly used antifungal agents[19,20].

The emergence of antifungal resistance represents a growing concern in the management of VVC, particularly in the context of pregnancy where treatment options are inherently limited due to safety considerations[21,22].Fluconazole, the most commonly prescribed oral antifungal agent for VVC, has demonstrated increasing resistance rates, with studies reporting resistance frequencies ranging from 23% to 62% among Candida isolates from pregnant women [23,24]. This resistance pattern is particularly pronounced among NAC species, with *C. krusei* showing intrinsic resistance to fluconazole and *C. glabrata* exhibiting dose-dependent susceptibility[25,26].

Tertiary care centers serve as important referral facilities for high-risk pregnancies and complicated gynecological conditions, making them ideal settings for studying the epidemiology and antimicrobial susceptibility patterns of VVC. These institutions typically encounter a diverse patient population with varying risk factors, including diabetes mellitus, immunocompromised states, and previous antifungal exposure, which may influence both the prevalence and resistance patterns of Candida species[27,28].

The implications of VVC during pregnancy extend beyond maternal discomfort, as several studies have suggested associations with adverse pregnancy outcomes, including preterm labor, premature rupture of membranes, chorioamnionitis, and congenital cutaneous candidiasis[29,30].These potential complications underscore the importance of accurate diagnosis, appropriate species identification, and targeted antifungal therapy based on susceptibility testing results[31,32].

Given the evolving epidemiology of VVC, increasing prevalence of antifungal resistance, and the unique challenges posed by pregnancy, comprehensive studies examining both the prevalence and antifungal susceptibility patterns of Candida species in pregnant women attending tertiary care centers are essential. Such investigations provide valuable insights into local epidemiological trends, guide empirical treatment strategies, and inform the development of evidence-based management protocols for this vulnerable patient population [33,34]

MATERIALS AND METHODS

Study Design: This was a cross-sectional study.

Place of Study: The study was conducted in the Department of Microbiology in collaboration with the Department of Microbiology & Obstetrics & Gynaecology at Maharaja Tukojirao Hospital, Indore.

Study Duration: The study was conducted over a period of 1 year, from October 2023 to September 2024, starting from the date of approval by the Institutional Scientific & Ethics Committee.

Study Population: Pregnant women attending the Obstetrics & Gynaecology Department who presented with clinical features of vulvovaginitis, such as itching, burning sensation, pain, inflammation, and excessive, stinging discharge, were enrolled in the study.

Sample Size: A minimum of 130 isolates were included.

Inclusion Criteria:

- Clinically suspected cases of vulvovaginitis among pregnant women.

Exclusion Criteria:

- Females not willing to provide consent.
- Patients on antifungal drugs.

Sample Collection:

Vaginal swabs were collected from pregnant women presenting with clinical features of vulvovaginitis and transported to the Microbiology Department within 2 hours, using sterile swab sticks with proper labeling.

Methodology

Collection & Transportation of Specimens:

Patients with clinical features of vulvovaginitis were informed about the study, and samples were collected after obtaining patient consent. The swab samples were transported to the laboratory within 2 hours, ensuring proper labeling.

Microbiological Processing of Samples:

1. **Direct Examination:**
   - **Gram's Staining:**
     - A smear was prepared from the vaginal swab, air-dried, and heat-fixed. It was stained with Crystal Violet, Gram's iodine, and decolorized with acetone. Counterstaining was done with Safranin, and the slide was examined under a microscope at 100x magnification.
     - **KOH Mount:**
     - The swab was mixed with 10% KOH in a test tube and incubated at 37°C for 30 minutes. The preparation was then mounted on a glass slide and examined under a microscope for budding yeast cells and pseudohyphae.
2. **Fungal Culture:**
   - **Culture Media:**
     - Sabouraud Dextrose Agar (SDA) with chloramphenicol was used to prevent bacterial contamination. Samples were inoculated on two sets of culture media and incubated at 25°C and 37°C to evaluate fungal growth.
3. **Identification of Isolates:**
   - **Culture Characteristics:**
     - The colonies were identified based on their color, shape, and texture. Different species of Candida, such as *C. albicans*, *C. tropicalis*, *C. krusei*, and *C. glabrata*, were identified based on their colony morphology.
   - **Germ Tube Test (GTT):**
     - The germ tube test was performed for the identification of *Candida albicans*. The test involved incubating yeast colonies in human serum at 37°C for 2-3 hours, followed by microscopic examination for germ tube formation.
   - **CHROM Agar Candida:**
     - CHROM Agar was used to identify different Candida species based on colony color. The isolates were incubated at 37°C, and the growth was observed after 24–48 hours.
4. **Morphological Characteristics on Dalmau Culture:**
   - Yeast colonies were streaked on cornmeal agar plates and incubated at 25°C for 3-5 days. The morphological features, such as hyphae, pseudohyphae, blastospores, and chlamydospores, were noted.
5. **Antifungal Susceptibility Testing:**
   - The isolates were subjected to antifungal susceptibility testing using fluconazole and voriconazole by the disc diffusion method, following the CLSI M44-A guidelines.
   - **Inoculum Preparation:**
     - The inoculum was prepared by subculturing yeast colonies and adjusting the turbidity to match the 0.5 McFarland standard. The suspension was streaked on Mueller Hinton Agar (MHA) supplemented with glucose and methylene blue.
   - **Disk Diffusion Method:**
     - Antifungal discs were placed on the inoculated agar plate and incubated at 35°C for 20-24 hours. The diameter of the inhibition zone was measured, and results were interpreted according to the established break-point criteria.
6. **Biofilm Detection by visual tube method:**

- Biofilm formation was assessed by incubating Candida isolates in Sabouraud Dextrose Broth (SDB) at 37°C for 24 hours. The cultures were stained with 0.1% Crystal Violet, and the presence of biofilm was observed as a visible film along the walls and bottom of the tube. Biofilm production was classified as weak (+), moderate (++), or strong (+++).

Visual tube method for biofilm production

RESULTS

The distribution of isolated Candida cases in obstetrics shows a higher prevalence in younger age groups, with the **26-35 years** group accounting for the largest proportion at **41%** (12 cases). The **15-25 years** age group follows closely, representing **37.7%** (11 cases). The occurrence of isolated Candida significantly decreases in older age groups, with only **14.62%** (3 cases) in the **36-45 years** group, and even lower percentages in the **46-55 years** (3.86%, 1 case) and **56-65 years** (1.53%, no cases) groups. The **>66 years** age group also shows no cases, highlighting a sharp decline in incidence as age increases. This suggests that younger women are more likely to experience Candida infections in obstetrics, with a notable decrease as age advances.

Table 1: Distribution of the Isolated Candida According to Age.

Age Group	Female (%)	Total No. of Cases
15-25 years	37.70%	11
26-35 years	41%	12
36-45 years	14.62%	3
46-55 years	3.86%	1
56-65 years	1.53%	0
>66 years	1.53%	0

The distribution of Candida isolates according to regional status shows a clear predominance in urban areas, with **80%** (48 cases) of the total obstetrics cases coming from urban regions. In contrast, **20%** (12 cases) of the isolates were from rural areas. This indicates a significantly higher prevalence of Candida infections in urban settings compared to rural ones within the obstetrics data.

Table 2: Distribution of the Isolates According to Regional Status.

Area	Total No. of Cases	Percentage (%)
Urban	48	80.00%
Rural	12	20.00%

The distribution of Candida isolates according to the patient's working profile reveals that the majority of cases are found among **unemployed** individuals, making up **66.67%** (40 cases) of the total obstetrics cases. **Skilled workers** account for **20%** (12 cases), while **unskilled workers** represent **13.33%** (8 cases). This suggests that unemployment is associated

with a higher prevalence of Candida infections in obstetrics, with a progressively lower incidence seen in skilled and unskilled workers.

Table 3: Distribution According to Patient's Working Profile Among the Isolated Candida (Obstetrics Data)

Worker Type	Total No. of Cases	Percentage (%)
Unemployed	40	66.67%
Skilled Worker	12	20.00%
Unskilled Worker	8	13.33%

The clinical features observed among isolated Candida patients in obstetrics indicate that **white discharge** is the most common symptom, affecting **83.33%** (50 cases) of the total patients. Other symptoms include **itching** in **16.67%** (10 cases), **foul smell** in **13.33%** (8 cases), and **burning sensation** and **abdominal pain**, both present in **1.67%** (1 case each). These findings highlight that white discharge is the predominant clinical feature, while other symptoms like itching and foul smell are less frequently reported.

Table 4: Clinical Features Among the Isolated Candida Patients.

Clinical Features	Total No. of Cases	Percentage (%)
White Discharge	50	83.33%
Itching	10	16.67%
Burning Sensation	1	1.67%
Foul Smell	8	13.33%
Abdominal Pain	1	1.67%

The distribution of co-morbidities among isolated Candida cases in obstetrics reveals that a significant portion of patients, **53.33%** (32 cases), have no co-morbidities. Among those with co-morbidities, **diabetes mellitus** is the most common, affecting **16.67%** (10 cases), followed by **anaemia** in **11.67%** (7 cases). Other co-morbidities include **hypertension** in **8.33%** (5 cases), **PLHIV** (people living with HIV) in **3.33%** (2 cases), and **tuberculosis** in **1.67%** (1 case). Additionally, **other conditions** such as thyroid disorders, preterm labor (PTL), and premature rupture of membranes (PROM) are present in **5%** (3 cases). These findings highlight that while many patients do not have co-morbidities, conditions like diabetes and anaemia are common among those with vaginal candidiasis (VVC).

Table5: Co-morbidities Associated with VVC Among the Isolates

Co-morbidity	Total No. of Cases	Percentage (%)
No Co-morbidity	32	53.33%
Diabetes Mellitus	10	16.67%
Anaemia	7	11.67%
PLHIV	2	3.33%
Tuberculosis	1	1.67%
Hypertension	5	8.33%
Others (Thyroid, PTL, PROM)	3	5.00%

The comparison of common co-morbidities among isolates in **gynaecology** and **obstetrics** shows distinct patterns between the two groups. **Diabetes Mellitus** is more common in **gynaecology isolates** (61.90%, 8 cases) than in **obstetrics isolates** (38.09%, 5 cases). **Anaemia** is predominantly seen in **obstetrics isolates** (85.71%, 6 cases), with a much lower prevalence in **gynaecology isolates** (14.28%, 1 case). Both groups report **PLHIV** (people living with HIV) as a co-morbidity, with **obstetrics isolates** showing a higher proportion (75%, 1 case) compared to **gynaecology isolates** (25%, 1 case). **Tuberculosis** is reported only in the **gynaecology isolates** (100%, 1 case), with no cases observed in the **obstetrics isolates**. These findings highlight differences in co-morbidities between gynaecology and obstetrics isolates, particularly with anaemia being more prevalent in obstetrics, while diabetes is more common in gynaecology.

Table 6: Common Co-morbidities Among Isolates

Co-morbidity	Gynaecology Isolates (%)	Obstetrics Isolates (%)
Diabetes Mellitus	8 (61.90%)	5 (38.09%)
Anaemia	1 (14.28%)	6 (85.71%)
PLHIV	1 (25%)	1 (75%)
Tuberculosis	1 (100%)	0

The microscopy positivity rate among the isolated Candida cases shows that **85%** (51 cases) of the samples tested positive in microscopy, while **15%** (9 cases) tested negative. This indicates a high correlation between microscopy results and culture positivity in the diagnosis of Candida infections.

Table 7: Microscopy Positivity Rate Among the Isolated Candida

Microscopy Result	Culture Positive (%)
Positive	51 (85.00%)
Negative	9 (15.00%)

The distribution of Candida species isolated in obstetrics cases shows that **C. albicans** is the most prevalent, accounting for **51.67%** (31 cases) of the total isolates. This is followed by **C. tropicalis**, which makes up **28.33%** (17 cases). Other species include **C. krusei** at **10%** (6 cases), **C. glabrata** at **8.33%** (5 cases), and **C. parapsilosis** at **5%** (3 cases). These findings indicate that C. albicans is the dominant species in obstetrics Candida infections, with C. tropicalis also being relatively common.

Table 8: Distribution of Candida Species Isolated

Candida Species	Total No. of Cases	Percentage (%)
C. albicans	31	51.67%
C. tropicalis	17	28.33%
C. glabrata	5	8.33%
C. krusei	6	10.00%
C. parapsilosis	3	5.00%

The distribution of Candida species as per their fluconazole susceptibility shows varying degrees of resistance and sensitivity. **C. albicans** has the highest sensitivity to fluconazole at **90.90%**, with **1.52%** classified as susceptible dose-dependent (SDD) and **7.58%** resistant. **C. tropicalis** also demonstrates good sensitivity at **83.80%**, with **8.10%** in both SDD and resistant categories. **C. glabrata** shows **77.80%** sensitivity, with **11.10%** in both SDD and resistant categories. **C. krusei** is not applicable for fluconazole susceptibility data, as no results are provided. **C. parapsilosis** exhibits complete sensitivity to fluconazole, with **100%** sensitivity and no resistance or SDD. This highlights the varied response of different Candida species to fluconazole, with **C. parapsilosis** showing the most favorable susceptibility profile.

Table 9(a): Distribution of Candida Species as per Fluconazole Susceptibility

Candida Species	Sensitive (%)	SDD (%)	Resistant (%)
C. albicans	90.90%	1.52%	7.58%
C. tropicalis	83.80%	8.10%	8.10%
C. glabrata	77.80%	11.10%	11.10%
C. krusei	-	-	-
C. parapsilosis	100%	0%	0%

The distribution of Candida species as per their voriconazole susceptibility reveals high sensitivity across all species tested. **C. albicans** shows **92.42%** sensitivity, with **7.58%** classified as susceptible dose-dependent (SDD) and no resistance. **C. tropicalis** exhibits **91.90%** sensitivity, with **8.10%** in the SDD category and no resistance. **C. glabrata**, **C. parapsilosis**, and **C. krusei** all show **100%** sensitivity, with no resistance or SDD cases reported. This indicates that

voriconazole is highly effective against most Candida species, with no resistance detected in **C. glabrata**, **C. parapsilosis**, and **C. krusei**, and minimal SDD in **C. albicans** and **C. tropicalis**.

Table 9 (b): Distribution of Candida Species as per Voriconazole Susceptibility

Candida Species	Sensitive (%)	SDD (%)	Resistant (%)
C. albicans	92.42%	7.58%	0%
C. tropicalis	91.90%	8.10%	0%
C. glabrata	100%	0%	0%
C. krusei	91.70%	8.30%	0%
C. parapsilosis	100%	0%	0%

The biofilm production rate among the isolated Candida species varies, with **C. tropicalis** showing the highest biofilm production at **48.64%** (17 cases). **C. albicans** follows closely with **36.36%** (31 cases) of isolates producing biofilms. **C. glabrata** has a biofilm production rate of **33.33%** (5 cases), while **C. parapsilosis** produces biofilms in **16.66%** (3 cases). **C. krusei** has the lowest biofilm production rate at **8.33%** (6 cases). These findings suggest that biofilm formation is more prevalent in **C. tropicalis** and **C. albicans**, which may influence the persistence and resistance of infections caused by these species.

Table 10: Biofilm Detection Among the Isolates

Candida Species	Total No.	Biofilm Producers (%)
C. albicans	31	36.36%
C. tropicalis	17	48.64%
C. glabrata	5	33.33%
C. krusei	6	8.33%
C. parapsilosis	3	16.66%

The relation between biofilm production and fluconazole resistance shows a notable association across different Candida species. For **C. albicans**, **80%** of the fluconazole-resistant strains produced biofilms, suggesting a potential link between resistance and biofilm formation. In **C. tropicalis**, all of the **fluconazole-resistant** strains (**100%**) were biofilm producers, indicating a strong correlation between biofilm production and fluconazole resistance in this species. Similarly, **C. glabrata** showed **100%** of its fluconazole-resistant strains producing biofilms, highlighting the role of biofilms in resistance. There were no fluconazole-resistant strains found for **C. krusei**, and **C. parapsilosis** had no fluconazole resistance, with **0%** biofilm production in its isolates. These findings underscore the significant association between biofilm production and fluconazole resistance, particularly in **C. albicans**, **C. tropicalis**, and **C. glabrata**.

Table 11: Relation of Biofilm Production and Fluconazole Resistance

Candida Species	Total Resistant Strains	Biofilm Production (%)
C. albicans	2	80%
C. tropicalis	3	100%
C. glabrata	1	100%
C. krusei	-	-
C. parapsilosis	0	0%

DISCUSSION

The presence of C. albicans observed in this study is consistent with many prior studies in the obstetric population. According to Malazy et al. C. albicans (44.21) was the most prevalent in vaginal infections, then C. lusitaniae (18.95) and C. parapsilosis (13.69) [35]. On the same note, a research carried out in Kota, Rajasthan established the C. albicans prevalence of 65.6% in pregnant women and 60.6% in non-pregnant individuals confirming its superiority in other geographical locations [36]. Nevertheless, other studies have suggested the opposite pattern, where Sangamithra et al. demonstrated a rather unexpected higher prevalence of non-albin Candida species (71) relative to C. albicans (29), with C. parapsilosis as the most common non-albin Candida species (41) in pregnant women [37].Resistance patterns of

fluconazole in this study are very similar to those reported worldwide. Wang et al. reported that C. glabrata had a much lower sensitivity to fluconazole (76.7) relative to C. albicans (98.2), C. tropicalis (98%), and C. parapsilosis (93.8) [38]. Likewise, in a case study conducted by Jain et al., the isolates of C. albicans exhibited 80% susceptibility to fluconazole in comparison to 53.3% fluconazole susceptibility in the isolates of non-albicans Candida species with the greatest resistance to fluconazole (46.7) of the NAC isolates [39]. The overall fluconazole susceptibility of C. parapsilosis in the present study is opposed to the latest outcomes of Thomaz et al. who reported fluconazole-resistant C. parapsilosis isolates with MICs of 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16 8-16The excellent results of voriconazole use against all Candida species are in agreement with various international studies.[40] Cuenca-Estrella et al. found low rates of voriconazole resistance in C. albicans (5%), C. parapsilosis (1.2%), and C. tropicalis (11) isolates, and higher MICs in C. glabrata and C. krusei [41]. Nonetheless, there are also regional differences, evidenced by the fact that Ghanem et al. discovered that 61.1% and 44.4% of the oral isolates of C. glabrata resistant to fluconazole and voriconazole respectively were found in drug users[42].The association between the formation of biofilms and fluconazole resistance is a critical result, which is consistent with the vast body of mechanistic study. Taff et al. have provided their multifactorial understanding of Candida biofilm resistance, which includes heightened activity of efflux pumps, components of extra-cellular matrix (β-glucan and extracellular DNA), and activation of stress response pathways [43]. They showed up to 1000-fold changes in antifungal resistance to be linked with biofilm formation and this result justified the clinical importance of biofilm-forming isolates in this experiment.These demographic trends of increased prevalence with decreasing age and linkage with diabetes mellitus are consistent with available epidemiological data. Moreira et al. particularly examined the presence of yeast infections in pregnant women with diabetes and observed much higher rates of Candida infection among diabetic pregnant women than among non-diabetic women [44]. It is assumed that the high concentration of progesterone and estrogen during pregnancy inhibits anti-Candida neutrophil and decreases the vaginal epithelial cell ability to inhibit C. albicans growth [44]. Falahati et al. found a strong relationship between candiduria and female gender, high fasting blood sugar, uncontrolled diabetes (HbA1 c ≥8), and acidic urine pH, and C. glabrata (50) and C. albicans (31.6) were the most frequent causative agents [45]. Socio-economic conditions that affect infection prevalence, such as increased prevalence in cities and in unemployed people, are indicators of wider access to health care and determinants related to hygiene that have been reported in other developing country contexts, but literature on specific comparative prevalence in obstetric Candida remains limited.

Clinical Implications

The findings underscore several critical clinical considerations. The resistance of biofilm formers to fluconazole will require routine testing of susceptibility to these antifungals and other agents such as voriconazole especially in the treatment of C. glabrata infections. The close relationship between diabetes mellitus and Candida infections highlights the need to consider diabetes mellitus in the prevention of recurrent cases. The fact that C. albicans and C. tropicalis are predominant biofilm producers indicates that empirical therapy must consider possible treatment resistance in these two species.

CONCLUSION

the evidence suggests the significance of awareness of the spread of the species, antifungal susceptibility and biofilm formation when treating Candida infections. The strong resistance of biofilm forming strains to fluconazole necessitates the use of other antimicrobial agents such as voriconazole especially against C. glabrata and C. tropicalis. The relationship between the production of biofilm and resistance indicates the importance of detection and intervention measures taken at an early stage to avoid the emergence of chronic and incurable infections.

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