



## Epidemiological profile and fluconazole susceptibility of patients with vulvovaginal candidiasis in northeast Iran

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### Abstract

**Background:** Vulvovaginal candidiasis (VVC) remains one of the most common infections of the female genital tract. This local study was conducted to identify the spectrum of *Candida* species associated with VVC and recurrent vulvovaginal candidiasis (RVVC) using different phenotypic and genotypic methods and assess their fluconazole susceptibility.

**Methods:** High vaginal swabs were collected from 576 patients with VVC. Swabs were subjected to KOH 10% and cultured on Sabouraud dextrose agar. The species identification of *Candida* isolates was made using phenotypic methods, including the germ tube test, corn meal agar (CMA), CHROMagar *Candida*, and PCR-RFLP as the best genotypic methods for confirmation of *Candida* species in vulvovaginal candidiasis. Fluconazole susceptibility testing was performed using the disk diffusion method.

**Results:** The data were analyzed using the chi-square test. The prevalence of candidiasis was 61%. The socio-demographic profile corresponded to a woman aged  $29.14 \pm 4.8$  years on average, pregnant (77%), diabetic (19%), with hypertension (10%), recurrent (9%), a history of fluconazole use (4%), and under 30 years of age (73%).

Vaginal swab cultures yielded *Candida* growth in 352 cases (61%). *Candida albicans* was the predominant isolated species (78%), while the most common non-*albicans* species were *C. glabrata* (14.7%), *C. parapsilosis* (4.2%), *C. tropicalis* (2.8%), and *C. krusei* (0.56%). Isolates of *C. glabrata* and *C. krusei* exhibited the highest rate of Double-Disk Synergy (DDS) resistance among all isolates tested.

**Conclusion:** *C. albicans* was the most common species. Careful periodical surveillance is needed to identify any changes in the susceptibility patterns to fluconazole with the increased use of this antifungal agent in Sayad Shirazi tertiary care hospital, Iran.

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### Introduction

Vulvovaginal candidiasis (VVC) is a disease caused by the abnormal growth of yeast in the vaginal mucosa, which has often been diagnosed in women's clinics in recent years (1).

Vulvovaginal candidiasis is caused by inflammatory changes in the vaginal epithelium due to infection with *Candida* species, most commonly *Candida albicans*. *Candida* is a part of the natural flora in many women and is often asymptomatic. Therefore, VVC requires the presence of *Candida* in the vagina and swelling, as well as symptoms of irritation, itching, disorientation, or inflammation (2,3).

Several reports have shown that the prevalence of candidiasis in Iran is remarkable and similar to the rest of the world (4-6). However, there are few reports on the sensitivity of antifungal drugs to vaginal isolates. In addition, some studies have shown that there are several treatments for VVC (7).

Based on several reports, resistance to fungi and relapses are serious problems among Iranian patients (8). In a study conducted in Qazvin, Iran, the authors believed that the difference between fluconazole and clotrimazole in recurrent candidiasis was not significant (9). Long-term treatment and increased use of antifungal drugs cause recurrent candidiasis in patients with vulvovaginal disease. Azoles have the benefit of being taken orally, which increases their ability (7,10).

This study aimed to estimate the prevalence of VVC diagnosis in women to identify the epidemiological profile and antifungal susceptibility to fluconazole in the Sayyad Shirazi Hospital, affiliated with Golestan University of Medical Sciences, northeastern Iran.

### Methods

This cross-sectional study was performed on 576 suspected vaginitis patients determined by a midwife or gynecologist, referred to Sayyad Shirazi Obstetrics and Gynecology Teaching Hospital, affiliated with Golestan University of Medical Sciences, Gorgan, Golestan Province (Iran) from 2020 to 2022. Information on age, medical history, symptoms, and recurrent VVC (defined as  $\geq 4$  episodes within a year) was collected (11). Vaginal secretions were collected from the posterior fornix with a sterile cotton swab and put into 3 mL of sterile saline.

Exclusion criteria included women currently menstruating, those who had intercourse in the last 24 hours, individuals who used vaginal creams in the week preceding the study, and those who had vaginal douching within 48 hours post-study. Additionally, individuals who had taken antifungal medication in the past

week (as indicated by negative *Candida* culture) were also excluded. All the specimens were cultured on CHROMagar *Candida* (CHROMagar *Candida*, France) for colony color and distinguishing concomitant *Candida* spp.

The identification was confirmed by germ tube formation, chlamydospore production in cornmeal agar (CMA) (Merck Germany) with 1% Tween 80, and cultured on Sabouraud dextrose agar (SDA; Merck, Germany) and incubated aerobically at 37 °C for 24-48 hours (7). *Candida* isolates were prepared for testing.

This study was conducted on 319 clinical samples from VVC obtained from 576 vaginal discharge specimens of women suspected of VVC that were sent to the Mycology Laboratory, Golestan University of Medical Sciences, Gorgan, Iran.

Ethical approval for the study was granted by the Golestan University of Medical Sciences Ethics Committee (Approval code: IR. GOUMS. REC. 1400.041).

The VVC isolates were cultured on SDA and then incubated aerobically at 37 °C for 24-48 hours (7). *Candida* isolates were identified by the morphological features on a culture medium, CHROMagar *Candida* (CHROMagar, Chrom, France), and definitive identification was achieved by polymerase chain reaction (PCR), employing specific primers (ITS1 and ITS4) (forward 5'-TCC GTA GGT GAA CCT GCG G-3') and ITS4 (reverse, 5'-TCC TCC GCT TAT TGA TAT GC-3') targeting the fungal 5.8s ribosomal RNA subunit, which is designed for the amplification of the zone of ITS1-5.8S-ITS2 rDNA duplicated using PCR and cut with MSP1(HpaII) enzyme. Production of restriction fragment length polymorphism (RFLP) performed by agarose gel electrophoresis (2).

We used a described disk diffusion by fluconazole (Rosco, France) assay for the susceptibility test of all yeast isolates (7,11,12). The test disks contained 25 µg. They were stored in a desiccator at 4°C. Initially, a yeast inoculum suspension adjusted to match a 0.5 McFarland density standard was prepared. A sterile cotton swab moistened with the inoculum suspension was used to apply to a 90-mm-diameter plate containing Mueller-Hinton agar supplemented with 2% glucose and 0.5 µg/mL methylene blue. The plates were allowed to dry for 5-15 minutes before a 10 µg/mL fluconazole disk was placed in the center of the agar. The plates were incubated for 18-24 hours at 35-37°C, and the slowly growing isolates could be read after 48 hours of incubation. A quality control (QC) strain, *C. albicans* ATCC 10231, with a recommended acceptable performance range of 32-43 mm, was tested once a week.

Reading and interpretation of zone diameter measurements were performed as follows: All inhibition zone diameters generated by disk diffusion tests were read and recorded by using the BIOMIC Plate Reader System (13), a semiautomatic electronic image-analysis system.

The interpretive breakpoints used for the fluconazole disk diffusion test were based on zones that correlated with the US National Committee for Clinical Laboratory Standards (NCCLS) recommended category breakpoints for the reference broth dilution method. Fluconazole breakpoints were S ≥19 mm, SDD =15-19 mm, and R ≤14 mm by CLSI-M44 indications (5,7).

Descriptive statistics were applied to all our data, using absolute numbers and percentages for qualitative variables and measures of central tendency (mean and standard deviation) for quantitative variables. The chi-square test was performed to explore the associations between variables and diagnosis of candidiasis, with the level of significance set to P < 0.05. A regression analysis was applied at 95% to determine the magnitude of the associations with the diagnosis of candidiasis. Analyses were performed using IBM SPSS Statistics v. 16 (IBM Corp., Armonk, NY, USA).

**Results**

In total, 576 vaginitis patients were included in the present study, of whom 317 patients aged 18-59 years showed vaginal candidiasis. Most of them were found in isolates of those aged 20-29 years old. Besides, 91% and 9% of cases were VVC and recurrent vulvovaginal candidiasis (RVVC) (Table 1). Those with positive candidiasis had underlying diseases such as diabetes (16%) and hypertension (10%), had a history of fluconazole use (4%), and pregnancy (70%) (Table 2).

**Table 1.** Distribution of *Candida* infection according to factors affecting the occurrence of infection

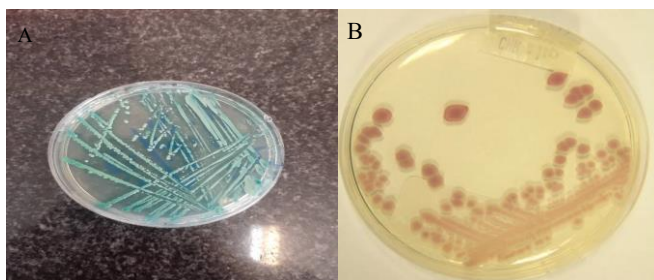
Risk factors	N (%)	Positive candidiasis	Negative candidiasis	Significance level
Diabetes	51(16%)	41 (13%)	10 (3%)	
Hypertension	32 (10%)	20 (6%)	15 (4%)	
History of fluconazole use	13 (4%)	12 (3%)	3 (1%)	
Pregnancy	221 (70%)	188 (59%)	28 (11%)	
Total	317 (100%)	261 (82%)	56 (18%)	< 0.001

**Table 2.** Distribution of *Candida* isolates in vaginal discharge samples according to age groups and the presence of VVC1 and RVVC2

Patient characteristics	Total				
	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. tropicalis</i>	<i>C. krusei</i>	Total
Age (y)					
> 20	30 (9.4%)	-	-	-	30 (9.4%)
20 - 29	150 (47.3%)	26 (8.2%)	3 (0.9%)	1 (0.3%)	180 (56.8%)
30 - 39	65 (20.5%)	21 (6.6%)	6 (2%)	1 (0.3%)	93 (29.3%)
40 - 49	7 (2.2%)	3 (0.9%)	1 (0.3%)	-	11 (3.5%)
50 - 59	2 (0.7%)	1 (0.3%)	-	-	3 (1%)
Total	254 (80.1%)	51 (16.1%)	10 (3.2%)	2 (0.6%)	317 (100%)
Vaginal candidiasis					
VVC	229 (72.2%)	48 (15.1%)	10 (3.01%)	2 (0.68%)	289 (91%)
RVVC	7 (2.2%)	17 (5.4%)	3 (1%)	1 (0.32)	28 (9%)
Total	236 (74.4%)	65 (20.5%)	13 (4.1%)	3 (1%)	317 (100%)

VVC: Vulvovaginal candidiasis; RVVC: Recurrent vulvovaginal candidiasis. Values are expressed as No. (%).

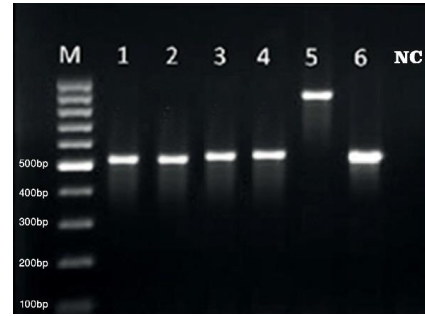
*C. albicans* produced green colonies on CHROMagar Candida chlamydospores on the CMA medium and appeared in the germ tube in the test, as well. CHROMagar Candida (CAC, Becton Dickinson, Heidelberg, Germany) is a differential ready-to-use chromogenic medium designed to identify *C. albicans*, *C. tropicalis*, and *C. krusei* by colony color and morphology. The colonies of *C. albicans* appear light to medium green, *C. tropicalis* colonies appear dark blue to metallic blue, and *C. krusei* appear pink with a whitish border (Figure 1).



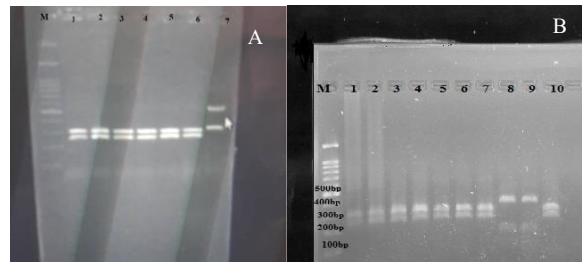
**Figure 1.** Morphology of *Candida* species in CHROMagar Candida medium. A. *C. albicans*, B. *C. glabrata*.

The clinical isolates and standard strain of *C. albicans* ATCC10231 produced bands with an approximate length of 535 bp (Figure 2). Digestion of the ITS region of *C. albicans* using the MSP1(HpaII) enzyme produced two bands of 297 and 338 bp (Figure 3).

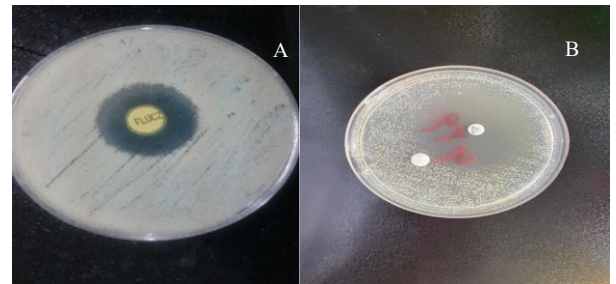
*C. albicans* strains were reported as susceptible S (Zone diameter ≥ 19 mm), susceptible dose-dependent (SDD) (15 to 18 mm), and resistant R (≤ 14 mm) (Figure 4).



**Figure 2.** Electrophoresis of bands from PCR of *Candida* isolates with primers ITS1-ITS4: lane 1 – *C. tropicalis* (524bp) lane 2 – *C. krusei* (510bp) lane 3 and 4 – *C. albicans* (bp535) lane 5 – *C. glabrata* (871bp) lane 6 – *C. albicans* standard (ATCC10231) (535bp) as positive control. NC as the negative control. M is a 100 bp ladder molecular size marker.



**Figure 3.** A. Patterns of PCR products of *Candida* isolates after digestion by the restriction enzyme HpaII. Lanes 1, *C. albicans* ATCC10231, 2-, and 6, *C. albicans*; (238, 297bp) and 7, *C. glabrata*; (314,557bp) B.1-7, and 10 *C. albicans*; 8,9, *C. tropicalis* (184, 340bp). Lane M is a 100 bp ladder molecular size marker.



**Figure 4.** Susceptibility pattern of *C. albicans* isolates to fluconazole (25 µg) showing different sizes of inhibition zone: (A) 14 mm (R), and (B) 22 mm (S).

We were able to identify 352 yeast isolates sequentially sent to our laboratory, including the following species: 274 *C. albicans* (14(4%) fluconazole-resistant), *C. glabrata* (22 (6%) fluconazole-resistant), *C. parapsilosis* (7 (2%) fluconazole-resistant), *C. tropicalis* (6 (1.7%) fluconazole-resistant) *C. krusei* (2 (0.7%) fluconazole-resistant) (5). The average inhibition zone diameters of fluconazole disk diffusion tests obtained with the different species of *Candida* are shown in (Table 3).

**Table 3.** Fluconazole category of susceptibility in 352 yeast isolates

Organism	Susceptible	Susceptibility dose-dependent	Resistant	Total (N)
	N %	N %	N %	
<i>C. albicans</i>	225 64%	35 10%	14 4%	274 (78%)
<i>C. glabrata</i>	20 6%	9 2%	22 6%	51 (14%)
<i>C. parapsilosis</i>	5 1.4%	3 0.8%	7 2%	15 (4%)
<i>C. tropicalis</i>	4 1.1%	-	6 1.7%	10 (3%)
<i>C. krusei</i>	-	-	2 0.56%	2 (0.56%)
S: Susceptible;	SDD: Susceptibility Dose-dependent;		R: Resistant	

**Discussion**

In this study, frequencies of different *Candida* species were separated; most of the *Candida* species among VVC were *C. albicans* isolates (68%, n = 274). Our findings are similar to the previously reported data by Sutra et al. (14). Bradfield Strydom et al. (2014) showed the best recovery of *Candida* genus in vaginal smear This may be due to processing more vaginal swab samples than high ones in our study urine smear (15).

In the study conducted by Williams et al., the youngest participant was a 1-year-old infant, while the oldest was 52 years old. *Candida* infection was found to be the highest in the age group of 21-40 years (16). In our study, the maximum isolation of *Candida* isolates was found in the age group of 18-49 years. The higher rate of fluconazole resistance in females to *Candida* isolates infection could be due to lower immunity and aging, which is similar to earlier studies reporting the rate of isolation of *Candida* isolates in females to be about 60% (6).

In the present study, *Candida* spp. was the most important agent of fungal vaginitis. This finding is in line with the findings of the previous studies that reported *C. albicans* and *C. glabrata* as the most frequent pathogenic yeasts in VVC patients (14,17,18). Several studies reported that the percentage of non-*Candida albicans* (NAC) isolates in vaginitis (7,19) and infections caused by unusual yeasts is on the rise (19). Traditional methods cause difficulties in the definitive diagnosis of the multiplicity of yeast species. Molecular approaches can improve the differentiation of less common yeast isolates and strongly similar yeast species such as those in *Candida* complexes. RFLP-PCR is most valuable for large epidemiological studies on unusual yeasts. It has been proved that the ITS1-5.8srDNA-ITS2 regions are an accurate approach for the definitive identification of pathogenic yeast species, particularly *C. glabrata* (14,19) and *C. parapsilosis* (20).

Mushi et al. (7) investigated *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* isolated from vaginitis patients and reported *C. albicans* as the main cause of vaginal candidiasis. Several studies conducted in Iran and other countries reported *C. albicans* as the predominant pathogen in VVC (6,15,18). Another study has reported *C. tropicalis* as the main species that causes VVC (21), which is not consistent with the current study that found *C. glabrata* to be the first and most frequently encountered NAC species.

Several studies mentioned *C. glabrata* as an important NAC species in *Candida* vaginitis patients (5,11,13). The current study revealed that *C. krusei*, as a NAC species, is associated with vulvovaginitis. Clinical isolates such as *C. krusei* and *C. glabrata* were resistant or showed low susceptibility to azole drugs, as reported by other studies (5,17). *C. glabrata* is reported as a common fungal pathogen in many countries and appears to be intrinsically resistant to fluconazole.

Other NAC species, such as *C. tropicalis*, *C. parapsilosis*, and *C. krusei*, were isolated from VVC and RVVC patients as well.

In the present study, VVC and RVVC patients were healthy women with a history of exposure to known risk factors such as diabetes, pregnancy, hypertension, and usage of fluconazole. According to clinical studies, most RVVC patients are diabetic women, and multiple recurring infections are often idiopathic without known potential risk factors (22). Numerous studies reported *C. albicans* as the most prevalent species, even more than NAC species, in vaginal candidiasis patients (22,23). Overall, *C. albicans* and NAC species had almost similar rates of prevalence (76% versus 24%, respectively). Since NAC species can often be found in RVVC patients and do not respond to standard antifungal therapies, their identification is of crucial importance. The results of this study indicated that *C. albicans* and *C. glabrata* are still the principal pathogenic agents in recurrent and non-recurrent *Candida* vaginitis.

Agar disk diffusion tests with antifungal drugs are not standardized, and a direct correlation between disk diffusion test results and clinical outcomes has not yet been reported. Consequently, antifungal disk diffusion tests should not be used as a guide for the selection and monitoring of antifungal therapy (6). However, considering that disk-diffusion assays are simple to perform and inexpensive, they may be a useful tool in large-scale surveys of clinical isolates to identify population distribution patterns of susceptibility to fluconazole (7,9-12).

As antifungal drug resistance may become more prevalent, it is increasingly important to evaluate current susceptibility profiles and emerging trends (2,19). In our study, most of the clinical yeast isolates were susceptible to fluconazole. However, it is clear that there are some species-specific differences in susceptibility to this antifungal agent. Notably, resistance rates to fluconazole ranged from 0 to 100% of the isolates tested, depending on the species of *Candida* considered for analysis. In agreement with data reported by other investigators (14,17-20), DDS resistance to fluconazole was most commonly reported among *C. glabrata* and *C. krusei* strains. Our data indicate that fluconazole has good in vitro activity against most clinically relevant strains of *Candida* spp.

## Conclusion

*C. albicans* and *C. glabrata* are the most important *Candida* species isolated from VVC and RVVC, which confirms the dramatic incidence of *Candida* species in VVC patients. Accurate identification of *Candida* spp. is important for treatment administration because some strains revealed different levels of resistance to antimycotic medicines.

Despite the difficulty in making a reliable estimate of this infection and its associated risk factors, we encourage the scientific community to continue their research on this increasing incidence worldwide to propose prevention strategies for potentially reversible determinants and improve health outcomes for the patients.

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University of Medical Sciences, Gorgan, Iran. The study was approved by the university's Ethics Committee (Code No. IR. GOUMS. REC. 1400.041).

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## Ethical statement

This study was approved by the ethics committee of the Golestan University of Medical (IR.GOUMS.REC.1400.041). All procedures were performed in accordance with the relevant guidelines and regulations.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Author contributions

SSH and RA conceived this study. SSH provided samples. SSH designed wet lab experiments. RA carried out wet lab experiments. SSH designed and performed computational analysis, prepared tables and figures, and interpreted the results. SSH and RA offered technical consultation and professional suggestions. SSH and RA wrote the manuscript. All the authors have read and approved the final manuscript.

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