



# What are the reasons for our lack of success in treating vaginitis despite our various empirical treatment approaches? Where are we going wrong?

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## ABSTRACT

**Objectives:** Vaginitis poses a significant challenge for women of all ages, impacting their quality of life. Clinicians struggle with diagnosis and management, facing treatment resistance and patient hygiene habits. We aimed to compare the effectiveness of vaginal and combined empirical treatments for vaginitis and identify factors contributing to treatment failure.

**Materials and Methods:** A retrospective cross-sectional study, incorporating both quantitative and qualitative approaches, was conducted on 369 patients who sought care at the gynecology outpatient clinic between 2021 and 2023 with complaints of vaginal infection. Empirical treatment was initiated after obtaining vaginal culture samples, and the diagnosis of vaginal candidiasis was confirmed through culture results. The specimens were collected at the gynecology outpatient clinic of Kafkas University Hospital. Comprehensive demographic information was gathered from all patients presenting with complaints of vaginal infection. The “daily hygienic behaviors questionnaire” was also administered, evaluated, and documented for each patient. The treatment responses of patients who presented to the clinic and were treated with two different empirical treatments, determined randomly by the attending clinician’s preference, were evaluated. In our clinic, empirical treatment involved either vaginal treatment with 750 mg metronidazole + 200 mg miconazole nitrate or a combination of vaginal 750 mg metronidazole + 200 mg miconazole nitrate and oral 150 mg fluconazole, administered based on the clinician’s choice.

**Results:** There was no statistically significant difference in the results of the two empirical treatments administered to the patients. There was no significant difference in demographic characteristics in the two treatment groups. Previous antibiotic use was significantly higher in the vaginal treatment group ( $p<0.05$ ). When the questionnaires questioning the personal hygiene habits of the patients with treatment failure were evaluated, erroneous habits that could explain this failure in treatment were revealed.

**Conclusion:** Candida infections, especially fluconazole-resistant strains, pose challenges. Access to microbiological testing and detailed medical histories is crucial. Patient education on culture-based treatment is essential. Addressing these challenges requires a sustainable solution.

**Keywords:** Antifungal treatment; *Candida albicans*; fluconazole; genital hygiene; pelvic infections; preventive medicine; sexually transmitted infections; vaginal discharge syndrome; vulvovaginal candidiasis; women’s health

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## INTRODUCTION

Issues pertaining to the vagina represent a frequent cause for patients to consult with obstetrician-gynecologists. These symptoms carry notable consequences, resulting in discomfort, pain, absenteeism from school or work, disturbances in sexual functioning, and impacts on self-image.<sup>1</sup>

The vaginal microbiome is complex and unique in comparison to that of anywhere else.<sup>2</sup> The vaginal microbiome experiences temporary changes due to menstruation, sexual activity, pregnancy, antimicrobial usage, hormonal therapies, perimenopause, and menopause.<sup>2,3</sup> It is predominantly characterized by *Lactobacillus*, an aerobic, Gram-positive rod.<sup>4</sup> *Lactobacilli* play a role in lactic acid and hydrogen peroxide production and help maintain a low vaginal pH. This acidic environment serves to reduce pro-inflammatory cytokines in the vagina and inhibit bacterial overgrowth.<sup>5</sup>

*Candida* is normally present in the genitourinary tract at colonization rates of 11.6-17%. *Candida* is a typically commensal microorganism in the genitourinary tract, with colonization rates ranging from 11.6% to 17%.<sup>6</sup> *Candida albicans* is responsible for over 70% of vulvovaginal candidiasis (VVC) cases affecting both the vulva and vaginal wall, followed by *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*.<sup>6-8</sup>

When local host defense mechanisms are compromised, candida can proliferate and cause a non-invasive infection known as VVC.<sup>6</sup> Frequent symptoms of *Candida* overgrowth in the vaginal area include an atypical odor, soreness, dysuria, dyspareunia, irritation, burning, itching, or changes in vaginal discharge.<sup>9,10</sup>

In Europe, VVC is a common cause of vaginitis, and in the United States, it ranks as the second most prevalent infection after bacterial vaginosis.<sup>6</sup> Epidemiological studies indicate that around 75% of women experience at least one VVC episode during their lifetime, with 40-45% having a second episode,<sup>8</sup> while 7-8% will develop recurrent VVC (RVVC), characterized by at least four confirmed episodes per year.<sup>6</sup>

Risk factors include diabetes mellitus, use of broad-spectrum antibiotics, factors like pregnancy or oral contraceptives, which will lead to increased estrogen levels causing an increase in glycogen content in vaginal secretion, immunosuppression, use of contraceptive device use (barrier methods), poor and wrong hygienic habits, certain sexual and clothing habits.<sup>6,11-14</sup>

Identifying *Candida* species and their susceptibility to antifungal agents is essential for effective therapy, especially since azoles are the most frequently prescribed class of antifungal drugs.<sup>6</sup> The main synthetic azole antifungal agents for VVC treatment are miconazole and fluconazole. These agents target the

lanosterol 14a-demethylase enzyme, which is critical for converting lanosterol to ergosterol, which is essential for *Candida* membrane integrity.

Insufficient treatment for vaginal *Candida* infection, along with antifungal drug resistance and patients' poor or incorrect hygiene practices, can lead to treatment failure. Our objective was to assess whether vaginal treatment alone or combined treatment methods, commonly used empirically for vaginitis in outpatient settings, exhibit superiority over one another and to identify factors contributing to treatment failure. The primary focus of this study was to pinpoint the factors responsible for treatment resistance in cases of VVC, even in situations where empirical treatment is administered.

## MATERIALS AND METHODS

A retrospective cross-sectional study, both quantitative and qualitative, was undertaken utilizing 369 vaginal swab samples obtained from female patients aged over 18 years experiencing signs and symptoms suggestive of vulvovaginitis during 2021 and 2023. The samples were collected at the Gynecology Outpatient Clinic of Kafkas University Hospital. Detailed demographic information was gathered, and the "Daily hygienic behaviors questionnaire results" from patients' records were assessed and subsequently performed. All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Kafkas University Faculty of Medicine, Ethics Committee of Clinical Trials (ethics approval reference number: 80576354-050-99/250). All procedures were performed according to the Declaration of Helsinki.

### Sample Collection

Participants were positioned in lithotomy for vaginal examination. A sterile swab stick was used to collect vaginal samples from the posterior fornix and vaginal walls after opening the labia with a speculum. Samples were transported to the lab in Amies medium for analysis and promptly transferred to the microbiology laboratory for further processing.

### Treatment and Follow-ups

The data were collected by reviewing patient files from clinicians who consistently follow similar monitoring procedures but employ different VVC treatment methods in their routine practice. These clinicians employed a random assignment method to allocate their patients to receive either exclusive vaginal treatment (750 mg metronidazole + 200 mg miconazole nitrate) or a combination of both vaginal and oral treatment (oral 150 mg fluconazole and vaginal 750 mg metronidazole

+ 200 mg miconazole nitrate). The data underwent analysis to evaluate treatment failure rates, make a comparison between the effectiveness of distinct treatments, and identify the variables associated with treatment failure during the 4-week follow-up assessments for patients who were administered either vaginal or combined (vaginal-systemic) treatment protocols following the clinicians' typical practice for VVC.

The study was conducted at the gynecology outpatient clinic, where patients receiving treatment for vaginitis were assessed through face-to-face questionnaires during their outpatient clinic visits. The questionnaires focused on the patients' genital hygiene habits as part of their daily routines. The primary objectives were to evaluate potential variances between two distinct empirical treatments for VVC commonly chosen by clinicians and to investigate the reasons for treatment failure in some patients, including potential factors like sexual behavior history, medical background, hygiene habits, or antibiotic resistance.

The demographic characteristics reported in the study included age, gravida, parity, education status, employment status, frequency of sexual intercourse, contraceptive methods, systemic disease, previous antibiotic use, and recurrent VVC and symptoms (Table 1). The patients were given a questionnaire to inquire about their genital hygiene habits.

### Statistical Analysis

Demographic information, including educational status, treatment, control culture results, and systemic diseases, was presented using numbers (n) and percentages (%). Cross-tabulations were employed, along with numbers (n), percentages (%), and the chi-square ( $\chi^2$ ) test statistics, to compare control culture results based on treatment status. Similarly, cross-tabulations were generated, and numbers (n), percentages (%), and chi-square ( $\chi^2$ ) test statistics were provided to compare categorical variables concerning control culture results.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 software were utilized for statistical analysis. A significance level of  $p < 0.05$  was considered statistically significant.

### RESULTS

Three hundred and sixty nine patients who sought care at the gynecology outpatient clinic with complaints of vaginal infection. The study included individuals with a mean age of  $31.86 \pm 17.80$  years. Among the participants, 58.9% had basic education, and 4.3% had no formal education. Furthermore, 82.4% (n=304)

Table 1. Demographic data	
	<b>All patients (n=369)</b>
Age (year) mean $\pm$ standard deviation	31.86 $\pm$ 17.80
Gravida mean (min-max)	3.0 (0-11)
Parity mean (min-max)	2.0 (0-11)
Education status, n (%)	
None	16 (4.3)
Primary	146 (39.6)
Middle	71 (19.3)
High	95 (25.7)
University	41 (11.1)
Employment, n (%)	
Not employed	304 (82.4)
Employed	65 (17.6)
*Symptoms, n (%)	
Discharge	339 (91.9)
Itching	236 (64.0)
Irritation & burning sensation	227 (61.5)
Dyspareunia	153 (41.5)
Bad odor	195 (52.8)
Vaginal discharge, n (%)	
Normal	63 (17.1)
Thin, grey	115 (31.4)
White, thick	189 (51.5)
Treatment, n (%)	
Vaginal	214 (58.0)
Orally + local	155 (42.0)
Control vaginal culture, n (%)	
Negative culture	292 (79.1)
Positive culture	77 (20.9)
Previous similar complaints, n (%)	
None	151 (40.9)
Exist	218 (59.1)
Sexual intercourse frequency, n (%)	
1-2 times a week	209 (56.6)
3-4 times a week	141 (38.2)
5 times or more a week	19 (5.1)
Contraception, n (%)	
OC	23 (6.5)
IUD	54 (15.2)
Monthly depot progestins	11 (3.1)
Calendar method	13 (3.7)
Condom	49 (13.8)
Withdrawal	45 (12.7)
BTL	14 (4.0)
None	145 (41.0)
Systemic disease, n (%)	
None	272 (73.7)
Exist	97 (26.3)
Complaints in the partner, n (%)	
None	273 (74.0)
Exist	96 (26.0)

were unemployed, while 17.6% (n=65) were employed. Vaginal discharge was the primary complaint in 82.3% of the patients who visited the outpatient clinic (Table 1).

The highest incidence of Candida isolation was noted among patients aged 20 to 29, whereas the lowest incidence was observed in patients aged 50 and above. According to the control culture results, no statistically significant difference was found in age groups ( $\chi^2=1.354$ ,  $p=0.716$ ) (Table 2).

Based on the results of the control culture, no statistically significant difference was found in terms of educational status ( $\chi^2=3.683$ ,  $p=0.451$ ) (Table 3).

According to the scanned data, it was observed that 155 patients received combined treatment (systemic and local), and 214 patients received vaginal treatment only in the outpatient clinic. Among individuals receiving vaginal treatment, 81.3% (n=174) showed no signs of growth in control vaginal cultures, while 18.7% (n=40) had. In contrast, among those who received a combined treatment, 76.1% (n=118) showed no growth in control vaginal cultures, while 23.9% (n=37) had. The study did not identify any statistically significant difference in control

culture results based on the two treatment methods received ( $\chi^2=1.460$ ,  $p=0.227$ ) (Table 4).

Analysis of questionnaires investigating the genital hygiene routines of women who did not have a chronic disease predisposing them to infection, such as immunodeficiency or DM, and yet experienced treatment failure, revealed statistically significant correlations with daily pad use, vaginal douching practices, preference for synthetic underwear and ironing habits (Table 5).

In the analysis of patients who received only vaginal treatment and did not achieve improvement in their follow-up clinic visits, it was determined that 3 women had a history of antibiotic treatment in the last 4 weeks, none of the women had a history of diabetes in their medical history, and rest of the women had incorrect hygienic practices as 31 of them used daily sanitary pads, 33 of them had vaginal douche habit, 15 of them preferred synthetic underwear usage, 9 of them described a habit of back to front bidet and all the women described a routine of pubic hair removal.

On the other hand, among the 40 patients who received combined treatment and did not achieve treatment success in their follow-up appointments, it was found that two of them had a history of antibiotic use in the last 4 weeks. Seven of the patients had a history of diabetes in their medical history. The rest of the women had incorrect hygienic practices as 22 of them used daily sanitary pads, 24 of them had vaginal douche habits, 16 of them preferred synthetic underwear usage, 8 of them described a habit of back to the front bidets and 28 of them women described a routine of pubic hair removal.

There has been a statistically significant difference in the use of vaginal douching according to educational status ( $\chi^2=10.532$ ,  $p=0.032$ ). Additionally, a statistically significant difference in pubic hair grooming has been identified based on educational status ( $\chi^2=37.882$ ,  $p=0.036$ ).

Furthermore, a statistically significant difference in daily pad usage has been detected based on age grouping ( $\chi^2=19.913$ ,  $p<0.001$ ).

Table 2. Comparison of age groups based on culture results					
	Growth in control culture			Test statistics	
	No growth (n=292)	Present (n=77)	$\chi^2$	p	
	n (%)	n (%)			
Age groups					
29 years and under	154 (52.7)	42 (54.5)	=1.354	0.716	
30-39 year	78 (26.8)	22 (28.6)			
40-49 year	43 (14.7)	11 (14.3)			
50 years and over	17 (5.8)	2 (2.6)			
$\chi^2$ : chi-square test statistics					

Table 3. Comparison of educational status based on culture results					
	Growth in control culture			Test statistics	
	No growth (n=292)	Present (n=77)	$\chi^2$	p	
	n (%)	n (%)			
Education status					
Illiterate	14 (4.8)	2 (2.6)	=3.683	0.451	
Primary	109 (37.3)	37 (48.1)			
Middle	57 (19.5)	14 (18.1)			
High	77 (26.4)	18 (23.4)			
University	35 (12.0)	6 (7.8)			
$\chi^2$ : chi-square test statistics					

Table 4. Post-treatment vaginal culture results				
	Treatment		Test statistic	
	Vaginal treatment (n=214)	Combined treatment (n=155)	$\chi^2$	p
	n (%)	n (%)		
Control culture				
No growth	174 (81.3)	118 (76.1)	=1.460	0.227
Growth exist	40 (18.7)	37 (23.9)		

**Table 5. Evaluation of genital hygiene questionnaire results together with control culture results**

	Control culture		Test statistic	
	No growth (n=292)	Growth exist (n=77)	$\chi^2$	p
	n (%)	n (%)		
Daily sanitary pads				
None	161 (55.1)	17 (22.1)	=26.670	<0.001
Exist	131 (44.9)	60 (77.9)		
Vaginal douche				
None	94 (32.2)	13 (16.9)	=6.936	0.008
Exist	198 (67.8)	64 (83.1)		
Underwear preference				
Cotton	165 (56.5)	42 (54.5)	=6.383	0.041
Synthetic	26 (8.9)	1 (1.3)		
Both	101 (34.6)	34 (44.2)		
Frequency of use of synthetic linen				
None	163 (55.8)	42 (54.5)	=15.849	0.001
1-2 times a week	45 (15.4)	23 (29.9)		
3-4 times a week	35 (12.0)	10 (13.0)		
More than 5 times a week	49 (16.8)	2 (2.6)		
Ironing lingerie				
Never	181 (62.8)	58 (75.3)	=7.087	0.029
Sometimes	59 (20.5)	15 (19.5)		
Always	48 (16.7)	4 (5.2)		
Pubic hair				
Do not interfere	6 (2.1)	0 (0.0)	=13.796	0.032
Waxing	116 (39.8)	34 (44.2)		
Shaving	133 (45.5)	40 (51.9)		
Trimming	1 (0.3)	1 (1.3)		
Laser	22 (7.5)	2 (2.6)		
Hair removal cream	12 (4.1)	0 (0.0)		
Waxing + trimming	2 (0.7)	0 (0.0)		

## DISCUSSION

VVC is a prevalent infection that affects millions of women each year, exerting a substantial adverse influence on the quality of their social and sexual well-being and is linked to noteworthy direct and indirect expenses.<sup>15</sup>

Limited data on the prevalence of VVC are accessible because the disease is not mandatory for reporting and is frequently self-

diagnosed without clinical and laboratory verification.<sup>1,16</sup> While vulvovaginal candida is not classified as a sexually transmitted infection, there is a higher likelihood that male partners may harbor the same Candida strain.<sup>1,16</sup> VVC seems to be more linked with orogenital rather than anogenital sexual activity.<sup>1,16</sup>

Complex infections are correlated with severe symptoms, the recurrence of non-albicans species more than three times annually in women dealing with uncontrolled diabetes, undergoing immunosuppressive therapy, compromised immunity or HIV, or during pregnancy.<sup>1,16</sup>

This study is important since diagnosis and treatment of VVC in low-to-middle-income countries are mostly done based on clinical presentations, without any laboratory diagnosis. The mean age of the study participants was  $31.86 \pm 17.80$  years, which correlates with the mean age of 31.5 years reported by Sasikala et al.<sup>17,18</sup> On the contrary, Amar et al.<sup>19</sup> reported a higher mean age of 37.3 years. Similar to Waikhom et al.'s<sup>18</sup> and other previous studies,<sup>17,19</sup> our research observed that the mean age of women comprising the patient population seeking treatment for vaginitis in our clinic was highest in the 20-29 age group followed by women aged 30-39. However, there was no statistically significant difference in age groups based on control culture results ( $\chi^2=1.354$ ,  $p=0.716$ ).

Similar to Bitew and Abebaw's<sup>20</sup> study, our research also found that most of the patient population consisted of women with only basic education who were not employed. A lower level of education and economic status may be linked to inadequate personal hygiene, potentially predisposing women to VVC. However, for the subset of women who received empirical treatment for vaginitis but did not experience its benefits, age, educational status, and economic status were not statistically significant.<sup>20</sup>

When post-treatment culture results were evaluated, candida was detected in 77 patients (20.86%) from both treatment groups. No statistically significant difference was observed between the treatment groups ( $p=0.22$ ). In this study, we observed similar efficacy of vaginal miconazole and combined vaginal miconazole plus oral fluconazole, which are preferred for empirical treatment of vaginitis. It was observed that fluconazole treatment was ineffective in 20.86% of our patients. The re-growth of *C. albicans* suggests that either resistance to the drug, misuse of the drug, or continuation of improper hygiene practices are possible. Although fluconazole has been used as a first-line empirical antimycotic drug for many years,<sup>18</sup> the failure to cure the infection in 20% of patients may be due to resistance to the drug, misuse, or poor personal hygienic habits. Whatever the reason, this is a very high percentage of treatment failure.

Therefore, the necessity of avoiding empirical treatment without waiting for culture results should be explained to patients with justification, and the patient's compliance with treatment should be increased.

### Study Limitations

The major limitation of our study is the small patient sample size and the retrospective nature of data collection. Redesigning the same study as a randomized controlled trial (RCT) would provide stronger support for the points the study aims to highlight. However, due to the unavailability of RCT ethics approval at our affiliated university, our study was designed retrospectively.

Although the number of patients in our study may not seem sufficient to generalize the results, all gynecologists working in the field, especially those dealing with recurrent vaginitis, will agree that our study primarily emphasizes the significant impact of daily lifestyle habits on the failures of medical treatment. In this area where preventive medicine is paramount, although our highlighted findings may need further support from additional studies, it is well-known to clinicians that it is crucial to make a difference by offering simple suggestions to patients and facilitating lifestyle changes.

### CONCLUSION

The management of vaginitis remains a complex issue for both women and clinicians. Vaginal and combination therapies, commonly chosen as empirical treatments, do not exhibit superiority in terms of efficacy. Clinically validated, effective treatments are now accessible through advancements in vaginal microbiome research and innovative therapeutic approaches. Women experiencing recurrent or complicated vaginitis must consult clinicians with specialized expertise in vaginitis rather than opting for empirical treatment. Emphasizing the significance of avoiding behaviors that may disturb vaginal flora is essential. To counteract the rise of drug resistance, we endorse the broad implementation of treatment strategies guided by culture antibiogram results instead of relying on empirical methods. Urgent measures are needed to heighten public awareness and restrict self-medication practices to tackle this issue effectively.

### ETHICS

**Ethics Committee Approval:** The study was reviewed and approved by the ethics committee of Kafkas University Faculty of Medicine, Ethics Committee of Clinical Trials (ethics approval reference number: 80576354-050-99/250). All procedures were performed according to the Declaration of Helsinki.

**Informed Consent:** All participants signed informed written consent before being enrolled in the study.

### Contributions

Surgical and Medical Practices: A.Y., M.C.; Concept: M.C.; Design: M.C.; Data Collection or Processing: A.Y., M.C.; Analysis or Interpretation: A.Y.; Literature Search: A.Y., M.C.; Writing: A.Y., M.C.

### DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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