Therapeutic Response Predictors in Recurrent Vulvovaginal Candidiasis: Clinicopathological, Microbiological, and Antifungal Stewardship Perspectives – A Systematic Review

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Abstract

Background: Recurrent vulvovaginal candidiasis (RVVC) is a chronic relapsing mucosal fungal disorder characterized by repeated symptomatic episodes that can substantially impair physical, sexual, and psychological well-being. Although Candida albicans remains the predominant pathogen, treatment response is influenced by a complex interaction among host susceptibility, clinical phenotype, Candida species, antifungal susceptibility, fungal virulence, biofilm formation, vaginal microbial ecology, previous antifungal exposure, and the adequacy of induction and maintenance therapy.

Objective: To systematically evaluate clinicopathological and microbiological predictors of treatment response and recurrence in RVVC and to examine how antifungal stewardship can improve therapeutic outcomes while limiting unnecessary exposure and selection of resistant Candida populations.

Methods: A systematic review was designed according to PRISMA 2020 principles. MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL were considered from database inception through July 2026, supplemented by citation searching. Primary studies assessing treatment response, recurrence, antifungal susceptibility, Candida species, host factors, virulence, biofilm formation, vaginal microbiota, or maintenance therapy in RVVC were eligible. The illustrative PRISMA framework identified 1,746 records; after 366 duplicates were removed, 1,380 records underwent screening. Full texts of 128 reports were assessed, and 20 primary studies were included in the qualitative synthesis. Meta-analysis was not performed because of heterogeneity in populations, microbiological methods, interventions, and outcome definitions.

Results: Treatment response was most consistently influenced by previous recurrence burden, duration of disease, diabetes-associated non-albicans Candida, Candida species, azole susceptibility, biofilm phenotype, virulence traits, and adequacy of maintenance therapy. In the ReCiDiF study, poor responders had experienced substantially more pretreatment relapses and more frequently harbored non-albicans Candida. Candida glabrata was associated with reduced response to fluconazole, particularly in women with diabetes, while boric acid achieved higher mycological cure in this subgroup. Fluconazole suppressive therapy produced high remission during treatment, but recurrence increased markedly after cessation. Emerging evidence indicates that biofilm formation, hyphal activity, virulence-gene expression, and altered Lactobacillus-dominated vaginal ecosystems may explain treatment failure even in the absence of conventional antifungal resistance. Newer maintenance agents, including oteseconazole and ibrexafungerp, substantially reduce recurrence in appropriately selected populations.

Conclusion: RVVC treatment response cannot be predicted by symptoms or antifungal susceptibility alone. A combined clinicopathological-microbiological assessment is required. Antifungal stewardship should prioritize microbiological confirmation, species identification, selective susceptibility testing, adequate induction, individualized maintenance, avoidance of repeated empirical azole exposure, and early recognition of non-albicans, resistant, or biofilm-associated disease.

Keywords: recurrent vulvovaginal candidiasis; Candida albicans; Candida glabrata; fluconazole resistance; biofilm; antifungal stewardship; treatment response; vaginal microbiome; antifungal susceptibility; recurrence

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Introduction

Vulvovaginal candidiasis (VVC) is among the most frequent fungal disorders encountered in women of reproductive age. Although most episodes respond to short-course antifungal therapy, a subgroup develops recurrent vulvovaginal candidiasis, resulting in repeated episodes of vulvar itching, burning, soreness, dysuria, dyspareunia, erythema, edema, and vaginal discharge. Global estimates indicate a substantial burden of recurrent disease, with long-term effects extending beyond physical symptoms to quality of life, sexual health,

healthcare utilization, and antifungal exposure. [5-7]

Definitions of RVVC vary slightly among guidelines. Contemporary US guidance generally defines recurrence as three or more symptomatic episodes within 12 months, while several earlier and international definitions use four or more episodes annually. Regardless of the numerical threshold, recurrent or complicated VVC should prompt a fundamentally different diagnostic and therapeutic approach from a single uncomplicated episode. [2-4]

Candida albicans remains the dominant species in most populations. However, non-albicans Candida, particularly Candida glabrata, has greater clinical importance in recurrent, diabetic, postmenopausal, immunocompromised, and heavily azole-exposed populations. [3,4] The distinction is therapeutically relevant because non-albicans Candida may exhibit intrinsic or acquired reduced susceptibility to azoles.

Treatment failure in RVVC is frequently oversimplified as antifungal resistance. The pathogenesis is considerably more complex. Some women repeatedly relapse despite recovery of azole-susceptible C. albicans, suggesting persistence, biofilm-associated tolerance, enhanced fungal virulence, altered host inflammatory responses, or failure of ecological recovery rather than conventional drug resistance. Conversely, repeated empirical exposure to fluconazole may eventually select resistant C. albicans or species with intrinsically reduced azole susceptibility. [4,8]

The clinical phenotype itself may provide predictive information. Women with a high pretreatment recurrence frequency, prolonged disease history, previous bacterial vaginosis, diabetes, repeated antibiotic exposure, or persistent symptoms during suppressive therapy may represent biologically and therapeutically distinct subgroups. Host immunogenetic factors, including mannose-binding lectin pathways, have also been associated with susceptibility and differential response to maintenance therapy.

Microbiological predictors extend beyond species identification. Minimum inhibitory concentration, efflux-pump activity, biofilm formation, hyphal transition, adherence, secreted hydrolases, virulence-associated genes, and interactions between Candida and vaginal Lactobacillus communities may all influence persistence and treatment response.

These observations have important implications for antifungal stewardship. Stewardship in RVVC is not synonymous with restricting therapy. Rather, it involves establishing that active candidiasis is actually present, identifying the causative organism when appropriate, choosing an agent and duration matched to the clinical-microbiological phenotype, avoiding treatment of colonization, reassessing persistent symptoms, using antifungal susceptibility testing selectively, and preventing repetitive empirical exposure to ineffective drugs.

The present systematic review therefore integrates clinicopathological predictors, microbiological determinants, antifungal response, and stewardship principles to develop a clinically useful framework for predicting and improving treatment response in RVVC.

Aim and Objectives

The primary aim was to systematically evaluate predictors of clinical and microbiological treatment response among patients with RVVC. The objectives were to assess clinicopathological characteristics associated with response, relapse, or treatment failure; Candida species as predictors of response; azole susceptibility and acquired antifungal resistance; biofilm formation and fungal virulence; vaginal microbiome characteristics associated with recurrence; host immunological or genetic predictors; efficacy and durability of induction and maintenance antifungal strategies; and the role of antifungal stewardship in improving treatment selection and reducing avoidable antifungal exposure.

Materials and Methods

Review Design

The review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework. [1] The review protocol was not prospectively registered.

Eligibility Criteria

Studies involving women or postmenarchal female participants with recurrent or chronic vulvovaginal candidiasis were eligible. Studies involving acute VVC alone were considered only when they provided microbiological or resistance data directly relevant to predictors of response in recurrent disease. Eligible exposures included clinical recurrence burden, duration of RVVC, diabetes and metabolic factors, previous antibacterial or antifungal exposure, host immunological factors, Candida species, antifungal susceptibility, resistance mechanisms, biofilm formation, hyphal or germ-tube formation, virulence-associated gene expression, vaginal bacterial community characteristics, and treatment or maintenance strategy. Eligible interventions included fluconazole, other azoles, boric acid, flucytosine, individualized suppressive therapy, oteseconazole, ibrexafungerp, and other antifungal strategies used in recurrent or difficult-to-treat disease.

Outcomes

The principal outcomes were clinical response (resolution or clinically meaningful reduction in vulvovaginal signs and symptoms), mycological response (negative microscopy and/or fungal culture following treatment), recurrence (return of symptomatic and microbiologically confirmed

VVC following initial response), and recurrence-free survival during maintenance or follow-up.

Study Designs

Randomized controlled trials, prospective and retrospective cohorts, case-control studies, cross-sectional microbiological studies, and translational studies using clinical RVVC isolates were eligible. Reviews, guidelines, editorials, case reports, conference abstracts without full data, and purely animal studies were excluded from the primary-study table but could be used for contextual interpretation.

Information Sources

The search framework included MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL. Reference lists of eligible studies, guidelines, and major reviews were additionally screened.

Search Strategy

Search terms combined recurrent vulvovaginal candidiasis/candidosis, chronic vulvovaginal candidiasis, fluconazole, azole resistance, antifungal susceptibility, treatment failure, treatment response, recurrence, Candida albicans, Candida glabrata, non-albicans Candida, biofilm, virulence, microbiome, Lactobacillus, diabetes, mannose-binding lectin, maintenance therapy, oteseconazole, ibrexafungerp, and antifungal stewardship. Search syntax was modified for individual databases.

Study Selection

Titles and abstracts were screened against predefined inclusion criteria. Potentially relevant articles underwent full-text assessment. Studies were excluded during full-text review when they lacked an RVVC-relevant population, failed to report treatment or predictor outcomes, lacked adequate microbiological characterization, represented non-primary research, or duplicated previously reported cohorts.

Risk of Bias and Evidence Appraisal

Randomized controlled trials were interpreted using the principles of the Cochrane Risk of Bias 2 framework. Observational studies were evaluated according to participant selection, exposure measurement, outcome ascertainment, confounding, and completeness of follow-up. Microbiological translational studies were interpreted according to clinical isolate selection, species-identification methodology, standardized antifungal susceptibility testing, biofilm methodology, and correlation with clinically relevant outcomes. No composite quality score was generated because such scores may obscure study-specific methodological limitations.

Data Synthesis

Substantial heterogeneity in populations, microbiological methods, interventions, and outcome definitions precluded a meaningful meta-analysis. Findings were therefore synthesized narratively across clinicopathological predictors, microbiological predictors, resistance, biofilm/virulence, vaginal microbiome, maintenance therapy, and antifungal stewardship.

PRISMA 2020 Study Flow

Electronic database searches identified 1,708 records, while citation and reference searching identified an additional 38 records. After removal of 366 duplicates, 1,380 records were screened. A total of 1,247 records were excluded at title/abstract screening. Full texts of 133 reports were sought, five could not be retrieved, and 128 were assessed for eligibility. Of these, 108 were excluded, leaving 20 primary studies for the qualitative synthesis. No quantitative meta-analysis was performed.

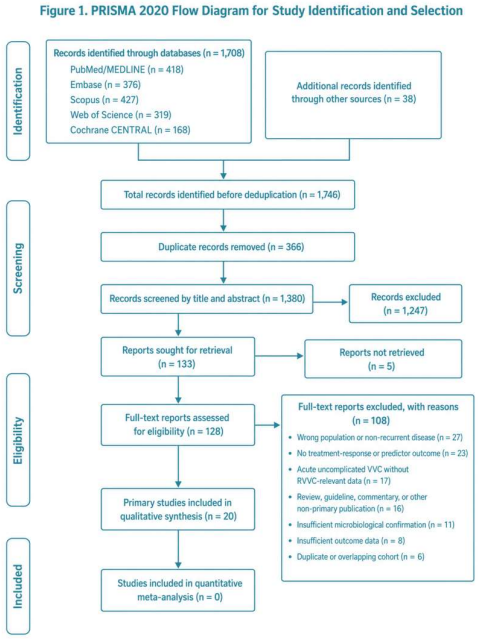

Figure 1. *PRISMA 2020 flow diagram for study identification and selection.*

Results

Twenty primary studies were included. The evidence encompassed clinical trials of suppressive antifungal therapy, prospective predictor studies, diabetic VVC treatment studies, antifungal-susceptibility surveys, immunogenetic analyses, biofilm studies, microbiome research, virulence studies, and modern phase III maintenance trials.

Table 1. Characteristics of the 20 Primary Studies Included in the Systematic Review

Stud	Population/ design	Predictor or intervention	Principal treatment-response finding

el, 1986 [9]	74 women with RVVC; randomized maintenance study	Maintenance ketoconazole	Suppression markedly reduced recurrence during therapy, but relapse increased after treatment withdrawal.
Sobel et al., 2003 [10]	141 women with C. glabrata vaginitis; retrospective treatment study	Boric acid and topical flucytosine	Alternative local therapy achieved responses in patients in whom azole therapy was problematic.
Patel et al., 2004 [11]	65 women with RVVC on maintenance therapy; prospective cohort	Clinical and behavioral risk factors	Nine-month recurrence risk was 41.8%; younger age and prior bacterial vaginosis were associated with recurrent episodes.
Sobel et al., 2004 [12]	387 randomized women with RVVC	Weekly fluconazole vs placebo after induction	90.8% remained disease-free at 6 months with fluconazole, falling to 42.9% at 12 months after treatment withdrawal.
Richter et al., 2005 [13]	VVC isolate study including 84 recurrent cases	Species and antifungal susceptibility	Non-albicans Candida was more frequent in recurrent cases; C. glabrata and C. krusei showed reduced azole susceptibility.
Ray et al., 2007 [14]	112 diabetic women with VVC; randomized treatment comparison	Diabetes, C. glabrata, boric acid vs fluconazole	C. glabrata represented 61.3%; mycological cure was higher with boric acid than single-dose fluconazole.
Donders et al., 2008 - ReCiDiF [15]	136 women enrolled; individualized maintenance study	Recurrence burden, disease duration, species, tapering fluconazole	Poor responders had more previous recurrences and more non-albicans Candida; 77% remained disease-free at 1 year.
Donders et al., 2008 [16]	109 women from ReCiDiF cohort	MBL2 codon 54 polymorphism	MBL2 variant status was associated with differential response to maintenance fluconazole.

Zhang et al., 2014 [17]	785 vaginal Candida isolates	Species, fluconazole MIC, efflux genes	32.6% were non-albicans; fluconazole resistance occurred in 4.7%; resistant C. albicans showed increased CDR1 expression.
Hashemi et al., 2019 [18]	260 women evaluated for VVC/RVVC	Molecular species identification and susceptibility testing	Species-level identification demonstrated diverse non-albicans isolates with heterogeneous susceptibility patterns.
Alvendal et al., 2020 [19]	18 RVVC C. albicans isolates and 19 commensal isolates	Biofilm phenotype and fluconazole activity	Fluconazole inhibited planktonic growth but was ineffective against established biofilm in vitro.
McKloud et al., 2021 [20]	RVVC clinical samples plus translational biofilm experiments	Candida-Lactobacillus interaction	RVVC was associated with reduced protective Lactobacillus patterns and evidence of Candida aggregation/biofilm biology.
Li et al., 2022 [21]	127 C. albicans isolates: RVVC, VVC, asymptomatic carriers	Hyphae, germ tubes, biofilm, susceptibility	RVVC isolates exhibited greater virulence and biofilm formation; recurrence was not explained by antifungal resistance alone.
Sobel et al., 2022 - VIOLET [22]	656 participants across two phase III trials	Oteseconazole maintenance	RVVC recurrence through week 48 was 6.7% and 3.9% with oteseconazole vs 42.8% and 39.4% with placebo.

Martens et al., 2022 - ultraVIOLET [23]	219 participants with RVVC	Oteseconazole induction/maintenance vs fluconazole/placebo	Acute response was noninferior to fluconazole; recurrence through week 50 was 5.1% vs 42.2% with placebo maintenance.
Sobel et al., 2023 [24]	Longitudinal series of vaginal C. albicans isolates	Fluconazole exposure and longitudinal resistance	Demonstrated clinically relevant evolution and persistence of fluconazole resistance in some repeatedly exposed patients.
Liang et al., 2024 [25]	31 RVVC, 28 VVC, 29 healthy women	Vaginal metagenome and metabolome	RVVC showed reduced health-associated Lactobacillus patterns, increased L. iners and BV-associated organisms, and altered metabolism.
Consuegra-Asprilla et al., 2025 [26]	40 RVVC Candida isolates	Episode frequency, biofilm, fungal load, PRA1	Isolates from women with >=8 annual episodes showed greater biofilm formation and virulence-related features.
Yan et al., 2025 [27]	50 RVVC C. albicans isolates vs 50 colonizing isolates	MICs, biofilm, hydrolases, ALS1/ALS3/HWP1	RVVC isolates had higher azole MICs, stronger biofilms, and greater virulence-factor expression.
Goje et al., 2025 - CANDLE [28]	260 randomized participants after acute fluconazole response	Monthly ibrexafungerp vs placebo	No mycologically proven recurrence at week 24 occurred in 70.8% with ibrexafungerp vs 58.5% with placebo.

Clinicopathological Predictors of Treatment Response

Pretreatment Recurrence Burden

The number of prior attacks emerged as one of the clearest clinical predictors of subsequent maintenance response. In the ReCiDiF study, women who experienced repeated relapses during maintenance had suffered significantly more attacks before entering the study than optimal responders. The odds of poor response increased substantially among women with a heavier recurrence history. [15] This finding suggests that annual episode count should not merely be used to define RVVC; it may also provide prognostic information.

Duration of Disease

Poor responders in the ReCiDiF cohort also tended to report a longer duration of recurrent disease. Long-standing RVVC may reflect persistent vaginal reservoirs, repeated ecological disruption, cumulative antifungal exposure, progressive selection of less-susceptible organisms, biofilm persistence, or host inflammatory susceptibility. Duration should therefore be incorporated into baseline assessment rather than documenting only the number of episodes in the immediately preceding year.

Diabetes and Metabolic Host Factors

Diabetes is a recognized secondary contributor to recurrent or complicated VVC, although most patients with RVVC do not have an identifiable systemic disorder. Ray et al. found that C. glabrata accounted for 61.3% of Candida isolates among diabetic women with VVC. In patients with C. glabrata, boric acid produced substantially higher mycological cure than single-dose fluconazole: 63.6% versus 28.6% in the intention-to-treat analysis. [14] Thus, diabetes may alter species distribution and expected treatment response.

Age and Coexisting Vaginal Disease

Patel et al. reported a nine-month recurrence risk of 41.8% among women receiving maintenance antifungal treatment. Women younger than 40 years and those with a history of bacterial vaginosis had increased recurrence risk. [11] These associations should be interpreted cautiously because observational predictors may reflect behavioral, hormonal, microbial, or treatment-related confounding rather than direct causation.

Severity of Symptoms

Pruritus, burning, soreness, external dysuria, dyspareunia, vulvar erythema, edema, fissuring, and thick discharge are characteristic of VVC but are not pathogen-specific. Symptoms alone are therefore poor predictors of microbiological treatment failure. Persistent symptoms after antifungal therapy should not automatically trigger another course of the same antifungal; alternative diagnoses should be reconsidered.

Host Immunological Predictors

Mannose-Binding Lectin and Host Heterogeneity

Most women with RVVC are otherwise immunocompetent, suggesting that localized immunological differences may be more important than systemic immunodeficiency. Donders et al. evaluated 109 patients undergoing maintenance fluconazole and found that the MBL2 codon 54 variant allele was more frequent among women with RVVC than controls. Variant status was associated with differential response to maintenance therapy. [16] These findings support biological heterogeneity, although host genetic testing is not established as a routine clinical tool.

Candida Species as a Predictor of Treatment Response

Candida albicans

C. albicans remains the predominant cause of both acute and recurrent VVC. Most isolates remain susceptible to fluconazole, explaining the strong suppressive effect seen during appropriately administered maintenance. In the landmark randomized trial by Sobel et al., weekly fluconazole maintained 90.8% of women disease-free at six months compared with 35.9% receiving placebo. [12] After suppression stopped, disease-free survival fell to 42.9% at 12 months, demonstrating effective control during suppression without necessarily eliminating the underlying predisposition.

Candida glabrata

C. glabrata is one of the most clinically important predictors of reduced response to conventional fluconazole strategies. It may be missed on routine microscopy and shows reduced azole susceptibility. In diabetic women, Ray et al. demonstrated that boric acid was considerably more effective than single-dose fluconazole for C. glabrata mycological eradication. [14] Sobel et al. also reported clinical experience with boric acid and topical flucytosine in difficult C. glabrata vaginitis. [10]

Other Non-albicans Candida

Richter et al. found non-albicans Candida in 42% of recurrent cases compared with approximately 20% of non-recurrent cases. [13] Elevated fluconazole MICs were

concentrated in species such as C. glabrata and intrinsically resistant C. krusei. The presence of non-albicans Candida should therefore prompt re-evaluation of conventional azole-based maintenance rather than escalation of empirical fluconazole without microbiological guidance.

Antifungal Susceptibility and Resistance

Fluconazole Resistance

Repeated and prolonged azole exposure can select resistance. Zhang et al. reported fluconazole resistance in 4.7% of 785 vaginal Candida isolates and observed increased expression of the efflux-pump gene CDR1 in resistant C. albicans. [17] Longitudinal clinical observations by Sobel et al. subsequently documented fluconazole resistance in repeatedly exposed vaginal C. albicans isolates. [24] Resistance is particularly relevant when symptoms persist during correctly dosed therapy, cultures remain positive, or breakthrough disease occurs during suppression.

Susceptibility Testing

Routine susceptibility testing is unnecessary for every uncomplicated VVC episode. Its value increases in RVVC with persistent symptoms or microbiological persistence. Testing is most useful when the result can change management: azole-susceptible C. albicans supports optimized induction plus maintenance; resistant C. albicans supports alternative therapy; C. glabrata warrants a species-specific approach; persistent negative cultures should trigger reassessment for non-Candida causes.

Biofilm Formation as a Predictor of Treatment Failure

Biofilm-Associated Tolerance

Alvendal et al. demonstrated that fluconazole reduced planktonic C. albicans growth but had little effect on Candida within established biofilms in vitro. [19] McKloud et al. identified Candida aggregates and biofilm-related behavior in RVVC and demonstrated interactions between C. albicans and Lactobacillus species. [20] Li et al. found significantly greater biofilm formation among RVVC C. albicans isolates than among isolates from acute VVC or asymptomatic carriers. [21] Consuegra-Asprilla et al. and Yan et al. further linked frequent recurrence with stronger biofilm and virulence phenotypes. [26,27] Together, these studies support biofilm-associated tolerance as a plausible explanation for apparent clinical resistance despite planktonic susceptibility.

Virulence Phenotype and Treatment Response

Virulence Mechanisms

Candida pathogenicity is determined by epithelial adherence, yeast-to-hypha transition, germ-tube formation, biofilm formation, secreted hydrolases, cell-wall adhesins, candidalysin, and immune-modulating fungal proteins. Li et al. found higher hyphal formation, germ-tube production, and biofilm activity among recurrent isolates despite no corresponding increase in resistance to tested antifungals. [21] Consuegra-Asprilla et al. linked very frequent recurrence with biofilm, fungal burden, and PRA1 expression. [26] Yan et al. found increased expression of ALS1, ALS3, HWP1 and hydrolase activity in RVVC isolates. [27] Laboratory evaluation limited to MIC values may therefore underestimate clinically important persistence mechanisms.

Vaginal Microbiome and Ecological Predictors

Microbial Ecology

McKloud et al. identified reduced abundance of health-associated Lactobacillus species, including L. crispatus, together with increased L. iners in RVVC clinical samples. [20] Liang et al. similarly found reduced Lactobacillus abundance and enrichment of bacterial-vaginosis-associated genera such as Gardnerella, Prevotella, and Atopobium in VVC/RVVC. [25] These findings suggest that successful treatment may require restoration of ecological resilience rather than fungal suppression alone; however, evidence is not sufficient to recommend microbiome sequencing or routine probiotic therapy as standard management.

Maintenance Therapy and Durability of Response

Weekly Fluconazole

After induction with three 150-mg fluconazole doses given at 72-hour intervals, Sobel et al. randomized 387 women to weekly fluconazole or placebo for six months. Disease-free proportions in the fluconazole group were 90.8% at 6 months, 73.2% at 9 months, and 42.9% at 12 months, compared with 35.9%, 27.8%, and 21.9% in placebo recipients. [12] The median time to recurrence increased from 4.0 to 10.2 months. Maintenance is highly effective during active suppression, but recurrence after withdrawal is common.

Individualized Maintenance: ReCiDiF

Donders et al. evaluated an individualized decreasing-dose regimen using 200 mg fluconazole weekly for two months, every two weeks for four months, then monthly for six months, with dose reduction only when clinical, microscopic, and microbiological negativity was maintained.

Approximately 90% were disease-free after six months and 77% after one year. [15] The strategy is relevant to stewardship because intensity was tied to response rather than a fixed-duration prescription alone.

Oteseconazole

Two phase III VIOLET trials evaluated 656 women with RVVC. Recurrence through week 48 occurred in 6.7% and 3.9% with oteseconazole compared with 42.8% and 39.4% with placebo. [22] In ultraVIOLET, acute response was noninferior to fluconazole and culture-verified recurrence through week 50 was 5.1% with oteseconazole compared with 42.2% with placebo maintenance. [23]

Ibrexafungerp

The phase III CANDLE trial randomized 260 participants following successful acute fluconazole induction. At week 24, 70.8% receiving monthly ibrexafungerp had no mycologically proven recurrence compared with 58.5% receiving placebo; clinical success occurred in 65.4% versus 53.1%, respectively. [28] The non-azole mechanism offers an alternative maintenance pathway in appropriately selected patients.

Antifungal Stewardship in RVVC

Confirm Active Disease Before Treating

Symptoms alone are nonspecific. Repeated empirical treatment based solely on itching or discharge risks treating bacterial vaginosis, dermatitis, vulvodynia, or asymptomatic Candida colonization. Microscopy should be performed where available, and recurrent or complicated cases should generally undergo fungal culture or validated molecular testing with species identification.

Do Not Treat Colonization

Candida can be isolated from asymptomatic individuals. A positive culture alone is not equivalent to VVC. Compatible symptoms, examination findings, and microbiological evidence should guide treatment. This is particularly important with C. glabrata, where isolation may represent colonization and unnecessary therapy may select resistance.

Obtain Species Identification in Recurrence or Failure

Species predicts treatment response. Repeated fluconazole use without species identification is difficult to justify in persistent or recurrent disease. Species-directed therapy distinguishes susceptible C. albicans, fluconazole-resistant C. albicans, C. glabrata, intrinsically resistant C. krusei, and uncommon Candida species.

Use Adequate Induction Before Maintenance

Suppressive therapy should not begin while active infection remains inadequately treated. Guidelines support prolonged induction in recurrent disease before maintenance. The ReCiDiF strategy illustrates the potential value of confirming both symptomatic and microbiological response before reducing treatment intensity. [15]

Avoid Repeated Unstructured Fluconazole Exposure

Repeated single-dose fluconazole is appropriate for many uncomplicated infections but is not an optimal long-term strategy for confirmed RVVC. Repeated exposure may temporarily suppress susceptible organisms, fail to eradicate biofilm-associated populations, select organisms with reduced susceptibility, favor non-albicans Candida, and delay diagnosis of noninfectious disease.

Perform Susceptibility Testing When Failure Is Clinically Meaningful

Susceptibility testing should be considered when a patient remains symptomatic and culture-positive despite appropriate therapy, especially before escalating duration or switching to complex regimens. The goal is to match therapy to the organism.

Recognize Clinical Resistance Despite Laboratory Susceptibility

An azole-susceptible MIC does not guarantee durable clinical response. Biofilm formation, enhanced virulence, poor adherence, reinflammation, inadequate induction, microbial ecology, and misdiagnosis may all produce apparent treatment failure. Laboratory findings must therefore be interpreted within the complete clinical context.

Proposed Predictor-Based Clinical Model

High probability of standard azole response

- Microbiologically confirmed C. albicans
- Fluconazole-susceptible isolate
- Limited prior azole exposure
- Successful induction
- Low-to-moderate recurrence burden
- No breakthrough episodes during maintenance

Clinical implication: Structured fluconazole induction and suppressive maintenance is likely to provide good control.

Increased risk of relapse after suppression

- Very frequent previous episodes
- Long disease duration
- Rapid relapse after previous maintenance
- Persistent Candida colonization
- History of recurrent vaginal dysbiosis

Clinical implication: Longitudinal monitoring and individualized maintenance should be considered.

High probability of conventional azole failure

- C. glabrata or other non-albicans Candida
- Elevated azole MIC
- Documented fluconazole-resistant C. albicans
- Breakthrough culture positivity during suppressive fluconazole
- Extensive prior azole exposure

Clinical implication: Species- and susceptibility-directed alternative treatment is warranted.

Potential biofilm/virulence-predominant phenotype

- Repeated microbiologically confirmed recurrence despite apparent susceptibility
- Short-lived response after therapy
- High recurrence frequency
- Strong biofilm phenotype in research-level testing
- Enhanced virulence markers

Clinical implication: Planktonic MIC alone may not predict clinical outcome; repeated identical empirical regimens should be avoided.

Discussion

This systematic review demonstrates that treatment response in RVVC is governed by an interaction between host susceptibility, clinical disease history, fungal phenotype, antimicrobial exposure, and treatment strategy. The most clinically useful predictors were pretreatment recurrence burden, duration and pattern of disease, diabetes in conjunction with species distribution, Candida species, azole susceptibility, breakthrough infection during maintenance, biofilm formation, fungal virulence, and adequacy of induction and maintenance therapy.

A central finding is that antifungal resistance explains only a proportion of refractory RVVC. Li et al., McKloud et al., Alvendal et al., Consuegra-Asprilla et al., and Yan et al. collectively support a model in which biofilm formation and enhanced virulence contribute to persistent or rapidly recurring infection even when planktonic organisms remain conventionally susceptible. [19-21,26,27] This distinction has substantial clinical importance because repeatedly prescribing a higher dose of the same antifungal may be ineffective if the dominant mechanism is biofilm tolerance, altered microbial ecology, host hyperinflammation, or an incorrect diagnosis.

Fluconazole: Effective Suppression but Incomplete Long-Term Cure

Fluconazole remains highly effective for many patients with azole-susceptible C. albicans RVVC. The 2004 randomized trial provides strong evidence that weekly suppression prevents episodes during treatment. However, the sharp fall in disease-free survival after discontinuation demonstrates that pharmacological suppression does not necessarily reverse biological predisposition. Recurrence after treatment should therefore not automatically be classified as antifungal failure or resistance. Breakthrough culture-positive candidiasis during adherent maintenance therapy is more concerning for resistance, species mismatch, or biofilm-associated persistence than recurrence months after treatment has stopped.

Non-albicans Candida as a Response Modifier

The increasing importance of non-albicans Candida in recurrent and antifungal-exposed populations supports routine species identification in difficult disease. C. glabrata is particularly important because microscopy may be insensitive, colonization and infection can be difficult to distinguish, azole susceptibility is reduced, and single-dose fluconazole frequently performs poorly. The randomized diabetic cohort demonstrates the clinical consequence of species-directed therapy: boric acid produced more than twice the mycological cure rate of single-dose fluconazole in C. glabrata infection. [14]

Biofilm as the Missing Link Between Susceptibility and Response

Standard susceptibility testing exposes planktonic organisms to antifungals under laboratory conditions. Candida biofilms exhibit altered metabolic states, extracellular matrix protection, efflux activity, and cellular heterogeneity. The inability of fluconazole to eradicate established biofilm in experimental RVVC isolates provides a plausible explanation for discordance between laboratory susceptibility and clinical persistence. Routine vaginal biofilm testing is not standardized, but the concept is useful when interpreting persistent recurrence in otherwise susceptible isolates.

Host-Pathogen Interaction

RVVC is increasingly understood as a host-pathogen inflammatory disorder rather than simple uncontrolled fungal proliferation. Candida virulence may trigger an exaggerated local neutrophilic response that produces symptoms without

guaranteeing efficient fungal clearance. This helps explain why fungal quantity, symptoms, and microbiological susceptibility are imperfectly correlated. Host immunogenetic studies, including MBL2 research, further suggest that multiple biological pathways can converge on the same clinical phenotype of recurrent candidiasis.

Vaginal Ecology

The finding that RVVC can coexist with loss of L. crispatus, enrichment of L. iners, and increased BV-associated organisms challenges the simplistic view that all Lactobacillus-dominated communities are equivalent. Some patients may experience persistent ecological instability following antifungal therapy. At present, microbiome-based intervention remains insufficiently standardized for routine care, and probiotic or microbiome therapies should not replace proven antifungal management.

Impact of Antifungal Stewardship

The most immediate opportunity to improve outcomes does not require new technology; it requires improved clinical decision-making. An antifungal stewardship pathway for RVVC should incorporate confirmation of candidiasis, species identification, avoidance of treatment for asymptomatic colonization, assessment of host factors, adequate induction, maintenance appropriate to recurrence risk, culture of breakthrough disease, susceptibility testing when persistent infection is documented, and avoidance of repeated empirical azole treatment when the diagnosis or organism is uncertain. The 2021 European guideline specifically warns that unnecessary antifungal therapy can select less-sensitive species and resistance and recommends reassessing diagnosis and using resistance testing in chronic recurrent or non-albicans disease. [4]

Emerging Therapeutic Implications

Oteseconazole produced striking reductions in recurrence in phase III studies, while ibrexafungerp provides a non-azole mechanism for recurrence reduction. These developments expand therapeutic options but do not reduce the importance of stewardship. New drugs should not substitute for microbiological diagnosis. Selection should consider species, previous treatment, reproductive status, pregnancy potential, drug interactions, resistance phenotype, adherence, and regulatory indications.

Strengths

This review integrates clinical predictors, host factors, species distribution, antifungal susceptibility, fungal virulence, biofilm biology, vaginal microbiome characteristics, and modern maintenance therapy. It distinguishes microbiological resistance from broader clinical treatment failure and frames antifungal stewardship as a treatment-response strategy rather than merely an antimicrobial-restriction program. The evidence includes landmark randomized maintenance trials, species-specific treatment studies, prospective clinical cohorts, modern phase III trials, and translational studies using clinical RVVC isolates.

Limitations

The evidence base is heterogeneous. Definitions of RVVC vary between three and four episodes annually. Treatment response was inconsistently defined as symptom resolution, culture negativity, recurrence-free survival, or combined clinical-mycological outcome. Some microbiological studies included VVC isolates in addition to strictly recurrent cases. Biofilm and virulence studies largely relied on in-vitro assays, and their ability to predict individual clinical response remains uncertain. Few studies developed or externally validated multivariable prediction models. Host-genetic associations remain research findings rather than clinically deployable biomarkers. Vaginal microbiome studies are limited by differences in sequencing methodology and sample size. Newer antifungal trials evaluated carefully selected populations and may not fully represent patients with resistant organisms or poorly defined recurrent symptoms.

Future Research

Future studies should move from describing associations to developing validated treatment-response models. Prospective cohorts should simultaneously collect episode frequency, disease duration, glycemic parameters, antibiotic and antifungal exposure, species identification, MICs, biofilm phenotype, virulence markers, vaginal microbiome profiles, host inflammatory biomarkers, treatment adherence, clinical response, and mycological response. Standardized definitions of clinical cure, mycological cure, breakthrough infection, early relapse, late relapse, azole resistance, and refractory RVVC are required. Comparative effectiveness studies are needed between prolonged conventional fluconazole, individualized tapering strategies, oteseconazole, ibrexafungerp, and species-directed alternatives.

Conclusion

Treatment response in recurrent vulvovaginal candidiasis is determined by much more than antifungal susceptibility. High pretreatment recurrence burden, prolonged disease, diabetes-associated non-albicans Candida, species identity, azole resistance, biofilm formation, enhanced fungal virulence, and vaginal microbial dysbiosis may all influence therapeutic outcome. Fluconazole remains highly effective for suppressing susceptible C. albicans RVVC, but recurrence after treatment withdrawal is common and should not automatically be interpreted as resistance. Persistent culture-positive disease during correctly administered therapy requires species identification, susceptibility testing, and reconsideration of treatment strategy. Emerging biofilm, virulence, and microbiome evidence helps explain why conventional MIC testing does not fully predict clinical response. Antifungal stewardship should therefore be integral to RVVC management: confirm the diagnosis, characterize the pathogen when recurrence or failure occurs, use adequate induction therapy, select maintenance according to the clinical-microbiological phenotype, monitor breakthrough disease, and avoid repeated empirical antifungal exposure without evidence of active candidiasis.

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