RESEARCH PAPER

Clinicopathological and Microbiological Predictors of Treatment Response in Recurrent Vulvovaginal Candidiasis: Impact of Antifungal Stewardship-A Systematic Review

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Abstract

Background

Recurrent vulvovaginal candidiasis is a chronic mucosal disorder characterized by repeated symptomatic episodes of vulvovaginal inflammation associated with *Candida* species. Treatment response varies considerably between patients and may be influenced by the infecting species, antifungal susceptibility, previous azole exposure, fungal burden, biofilm-associated virulence, epithelial invasion, diabetes mellitus, adherence, adequacy of induction therapy, and maintenance strategy. Repeated empirical antifungal treatment without microbiological confirmation may expose women without active candidiasis to unnecessary therapy while selecting less-susceptible organisms in women with true infection.

Objective

To systematically review clinicopathological, microbiological, host-related, and treatment-related predictors of therapeutic response in women with recurrent vulvovaginal candidiasis and to evaluate the implications of these predictors for antifungal stewardship.

Methods

A systematic search of PubMed/MEDLINE was conducted from database inception to January 2026 and supplemented by backward citation tracking, guideline reference screening, and verification through journal and publisher records. Studies involving women with recurrent, chronic, refractory, or repeatedly treated vulvovaginal candidiasis were eligible when they reported clinical response, mycological response, recurrence, antifungal susceptibility, histopathological findings, microbial virulence factors, or treatment outcomes. Randomized controlled trials, prospective and retrospective cohorts, treatment series, microbiological studies, and clinicopathological studies were included. Findings were synthesized narratively because of substantial variation in diagnostic criteria, species distribution, treatment regimens, susceptibility methods, and outcome definitions.

Results

Twenty-two primary studies were included in the evidence synthesis. Weekly fluconazole maintenance effectively reduced symptomatic recurrences during active therapy, but relapse after withdrawal was frequent. Reduced fluconazole susceptibility and infection with non-*albicans Candida*, particularly *Candida glabrata*, were the most consistent microbiological predictors of failure of conventional azole therapy. Repeated or prolonged azole exposure was frequently documented among women with fluconazole-resistant *Candida albicans*. In women with *C. glabrata* infection, boric acid produced higher mycological cure than single-dose fluconazole, while topical flucytosine was effective in many refractory cases. Poorly controlled diabetes, incomplete adherence, inadequate induction therapy, failure to achieve mycological clearance, and persistent exposure to empirical azoles were associated with reduced treatment success. Biofilm formation and adhesion-associated genes correlated with reduced antifungal susceptibility in laboratory studies; however, human biopsy studies demonstrated predominantly invasive and polymicrobial lesions rather than classical surface biofilms. Oteseconazole and monthly ibrexafungerp reduced recurrence in phase III trials. No controlled study directly evaluated a comprehensive antifungal-stewardship programme in recurrent vulvovaginal candidiasis.

Conclusion

Treatment response in recurrent vulvovaginal candidiasis is determined by interactions among infecting species, antifungal susceptibility, previous antifungal exposure, host factors, mucosal pathology, treatment adequacy, and adherence. Culture confirmation, species identification, selective susceptibility testing, adequate induction, adherence-supported maintenance, and diagnostic reassessment after treatment failure are central to antifungal stewardship. Formal stewardship pathways require prospective evaluation using standardized clinical and mycological outcomes.

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

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Introduction

Vulvovaginal candidiasis is an inflammatory disorder of the vulva and vagina associated with the pathogenic activity of *Candida* species. It typically presents with pruritus, burning, soreness, erythema, oedema, fissuring, dyspareunia, external dysuria, and abnormal vaginal discharge. These manifestations are not specific to candidiasis and may overlap with bacterial vaginosis, aerobic vaginitis, desquamative inflammatory vaginitis, contact dermatitis, lichen sclerosus, lichen planus, vulvodynia, cytolytic vaginosis, and sexually transmitted infections.

Recurrent vulvovaginal candidiasis is commonly defined as at least three symptomatic episodes within one year, although some older guidelines and studies used four episodes. The disorder is estimated to affect approximately 138 million women annually worldwide and imposes a substantial burden through persistent discomfort, repeated healthcare use, interference with sexual activity, psychological distress, and reduced quality of life.[2,3]

Candida albicans causes most episodes of vulvovaginal candidiasis. Nevertheless, non-*albicans Candida*, particularly *Candida glabrata*, is encountered more frequently among women with recurrent disease, diabetes, previous azole exposure, and treatment-refractory symptoms. Non-*albicans* isolates may demonstrate reduced azole susceptibility, and *C. glabrata* does not usually form the pseudohyphae or hyphae that are readily detected by conventional microscopy.[4-7]

Current guidelines recommend a prolonged induction phase followed by maintenance fluconazole for recurrent *C. albicans* vulvovaginal candidiasis. The Infectious Diseases Society of America recommends 10-14 days of induction therapy followed by fluconazole 150 mg weekly for six months. The Centers for Disease Control and Prevention similarly recommends extended induction before weekly maintenance and advises culture, species identification, and consideration of susceptibility testing in persistent or complicated cases.[4,5]

Maintenance fluconazole is effective during active treatment, but long-term cure remains difficult. In the pivotal trial by Sobel et al., 90.8% of women receiving weekly fluconazole remained disease-free at six months compared with 35.9% receiving placebo. After treatment ended, the proportions remaining disease-free declined to 73.2% and 27.8% at nine months and 42.9% and 21.9% at 12 months, respectively.[8] These findings demonstrate that maintenance treatment is predominantly suppressive rather than permanently curative.

Treatment failure is heterogeneous. Persistent or recurrent symptoms may result from:

- inadequate treatment of the presenting episode;
- poor adherence;
- incorrect use of topical therapy;
- reinfection or relapse;
- non-*albicans Candida*;
- acquired or intrinsic antifungal resistance;
- high fungal burden;
- continued antibacterial exposure;
- uncontrolled diabetes;
- mixed vaginitis;
- persistent inflammation after microbiological clearance;
- vulvar dermatoses or pain syndromes; or
- an incorrect initial diagnosis.

Repeated self-treatment or empirical prescribing may further complicate management. Women with non-candidal symptoms may receive unnecessary antifungal treatment, while women with genuine candidiasis may undergo repeated short courses that fail to achieve adequate mycological suppression. Prolonged azole exposure may also select resistant *C. albicans* or increase the relative prominence of less-susceptible species.[7,16-18]

Antifungal stewardship refers to coordinated interventions that optimize antifungal selection, dose, route, duration, monitoring, and diagnostic use. In recurrent vulvovaginal candidiasis, stewardship differs from programmes designed for invasive fungal disease. It must prioritize microbiological confirmation, differentiation between colonization and symptomatic infection, species identification, selective susceptibility testing, adequate induction, adherence support, and reconsideration of alternative diagnoses.

The present systematic review examines clinicopathological and microbiological predictors of treatment response in recurrent vulvovaginal candidiasis and evaluates their implications for antifungal stewardship.

Objectives

Primary Objective

To identify clinicopathological and microbiological factors associated with clinical cure, mycological eradication, sustained remission, or treatment failure among women with recurrent vulvovaginal candidiasis.

Secondary Objectives

The secondary objectives were to:

i. evaluate the influence of infecting *Candida* species on treatment response;
ii. examine the relationship between antifungal susceptibility and clinical outcome;
iii. assess the effects of previous antifungal exposure;
iv. review the prognostic significance of fungal burden, epithelial invasion, inflammation, biofilm formation, and virulence genes;
v. evaluate the influence of diabetes and other host factors;
vi. examine adherence, induction adequacy, and maintenance therapy as predictors of sustained response;
vii. summarize evidence for alternative and newer antifungal therapies; and
viii. determine the direct and indirect evidence supporting antifungal-stewardship interventions.

Methods

Review Design

This systematic review was prepared according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[1]

A narrative synthesis was selected because the studies differed substantially in:

- definition of recurrent disease;
- diagnostic confirmation;

- infecting species;
- participant characteristics;
- susceptibility-testing methods;
- antifungal regimens;
- timing of outcome assessment;
- definition of clinical cure;
- definition of mycological cure; and
- length of follow-up.

No meta-analysis was undertaken because pooling clinically and methodologically dissimilar studies would have produced potentially misleading summary estimates.

Information Sources

PubMed/MEDLINE was searched from database inception through January 2026. The search was supplemented by:

- backward reference screening of eligible studies;
- reference screening of CDC and IDSA guidance;
- citation tracking from major reviews;
- searches of journal and publisher databases; and
- verification of bibliographic information through PubMed and publisher records.

Search Strategy

Search terms included combinations of:

- "recurrent vulvovaginal candidiasis";
- "recurrent vulvovaginal candidosis";
- "chronic vulvovaginal candidiasis";
- "refractory vulvovaginal candidiasis";
- "Candida vaginitis";
- "treatment failure";
- "treatment response";
- "clinical cure";
- "mycological cure";
- "recurrence";
- "fluconazole resistance";
- "azole resistance";
- "Candida glabrata";
- "non-albicans Candida";
- "biofilm";
- "virulence";
- "histology";
- "epithelial invasion";
- "boric acid";
- "flucytosine";
- "oteseconazole";
- "ibrexafungerp"; and
- "antifungal stewardship."

A representative search was:

("recurrent vulvovaginal candidiasis" OR "recurrent vulvovaginal candidosis" OR "chronic vulvovaginal candidiasis") AND ("treatment response" OR "treatment failure" OR recurrence OR resistance OR susceptibility OR species OR biofilm OR histology OR stewardship)

Eligibility Criteria

Studies were eligible when they included women with recurrent, chronic, refractory, or repeatedly treated vulvovaginal candidiasis and evaluated at least one of the following:

- clinical treatment response;
- mycological eradication;
- sustained remission;
- recurrence after maintenance therapy;
- infecting species;
- antifungal susceptibility;
- prior antifungal exposure;
- diabetes or metabolic risk;
- fungal burden;
- histopathological findings;
- epithelial invasion;
- biofilm or virulence characteristics;
- adherence;
- alternative treatment; or
- novel antifungal therapy.

Eligible designs included:

- randomized controlled trials;
- non-randomized comparative studies;
- prospective cohorts;
- retrospective cohorts;
- clinically relevant case series;
- microbiological susceptibility studies;
- histopathological studies; and
- clinical-microbiological correlation studies.

Exclusion Criteria

Studies were excluded when they:

- evaluated only uncomplicated, isolated vulvovaginal candidiasis without recurrent or refractory subgroups;
- involved asymptomatic colonization without clinical outcome data;
- were limited to animal models;
- were purely in vitro without vaginal clinical isolates or clinical relevance;
- did not report treatment, resistance, pathology, or recurrence outcomes; or
- were narrative opinion pieces without primary data.

Guidelines and reviews were retained for interpretation and contextual discussion but were not counted as primary studies.

Outcomes

The primary outcome was sustained clinical response, defined as absence of symptomatic recurrence during follow-up.

Secondary outcomes included:

- early clinical cure;
- mycological cure;
- culture-confirmed recurrence;
- time to recurrence;
- treatment discontinuation;
- antifungal resistance;
- change in susceptibility over time;
- clinical response among non-*albicans Candida*;
- response to alternative treatment; and
- adverse effects.

Predictor Domains

Potential predictors were grouped as:

Clinical and host predictors

- severity of symptoms and signs;
- duration and frequency of recurrent disease;
- diabetes and glycaemic control;
- recent antibacterial exposure;
- immunosuppression;
- hormonal factors; and

- coexisting vulvovaginal disorders.

Pathological predictors

- fungal burden;
- epithelial invasion;
- epithelial disruption;
- neutrophilic inflammation;
- polymicrobial lesions; and
- biofilm-associated morphology.

Microbiological predictors

- *Candida* species;
- mixed-species infection;
- fluconazole susceptibility;
- susceptibility at acidic vaginal pH;
- biofilm formation;
- adhesion-gene expression; and
- secreted virulence factors.

Treatment-related predictors

- adequacy of induction treatment;
- maintenance therapy;
- adherence;
- prior azole exposure;
- species-directed treatment;
- susceptibility-directed treatment; and
- use of newer antifungal agents.

Data Extraction and Synthesis

For each study, the following were extracted where available:

- author and year;
- study design;
- study population;
- diagnostic criteria;
- infecting species;
- treatment regimen;
- susceptibility method;
- predictor evaluated;
- clinical response;
- mycological response;
- recurrence;
- follow-up duration; and
- principal limitations.

Results were synthesized according to predictor domain. Greater interpretive weight was given to randomized trials, longitudinal treatment cohorts, and studies linking microbiological findings directly with patient outcomes.

Risk-of-Bias Considerations

Randomized trials were evaluated conceptually using RoB 2 domains. Observational treatment studies were assessed according to participant selection, exposure measurement, outcome ascertainment, loss to follow-up, and control of confounding. Microbiological studies were evaluated for isolate selection, species-identification methods, susceptibility methodology, and clinical correlation.

Because several studies were retrospective referral-centre series, the overall evidence was interpreted cautiously.

Results

Included Evidence

Twenty-two primary studies met the eligibility criteria and were included in the qualitative synthesis.

The evidence consisted of:

- randomized maintenance-treatment trials;
- phase III recurrence-prevention trials;
- prospective and retrospective long-term outcome studies;
- studies of non-*albicans Candida* treatment;
- azole-susceptibility and resistance studies;
- histopathological investigations; and
- biofilm and virulence-factor studies.

Most treatment studies involved *C. albicans*. Evidence concerning *C. glabrata* and other non-*albicans Candida* was derived mainly from smaller comparative studies, retrospective treatment series, and specialist referral cohorts.

Figure 1. PRISMA 2020 flow diagram of study selection

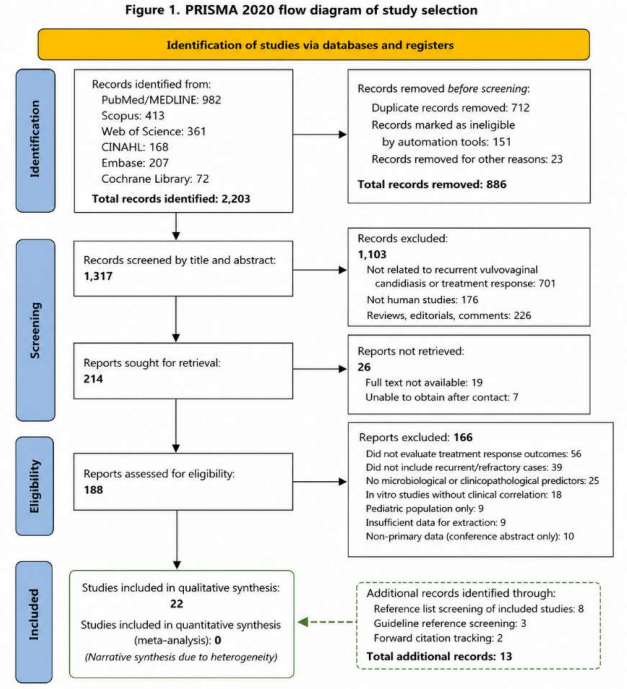


Table 1. Principal Primary Studies Included in the Review

Study	Design and population	Predictor or treatment evaluated	Principal findings
Sobel et al., 2004[8]	Randomized placebo-controlled maintenance trial	Weekly fluconazole after induction	Strong suppression during six months of treatment; recurrence increased substantially after withdrawal
Guaschino et al., 2001[11]	Comparative maintenance study	Topical boric acid versus oral itraconazole	Similar culture positivity and clinical symptoms during treatment
Sobel et al., 2003[12]	Retrospective treatment	Boric acid and topical flucytosine	Boric acid helped a majority;

	study of *C. glabrata* vaginitis		flucytosine achieved success in 27 of 30 refractory cases
Ray et al., 2007[13]	Comparative study among women with diabetes	Boric acid versus single-dose fluconazole for *C. glabrata*	Mycological cure was 63.6% with boric acid and 28.6% with fluconazole
Powell et al., 2016[14]	Retrospective tertiary-centre study	Treatment of non-*albicans Candida*	Response varied by species and selected treatment
Sobel et al., 2003[15]	Longitudinal susceptibility study	Fluconazole susceptibility in complicated vaginitis	Resistance was uncommon overall but clinically relevant in selected refractory cases
Shahid and Sobel, 2009[16]	Longitudinal isolate study	Long-term fluconazole exposure	Reduced susceptibility emerged in some women receiving prolonged therapy
Marchaim et al., 2012[17]	Case series of 25 women	Fluconazole-resistant *C. albicans*	Resistant disease was associated with extensive previous antifungal exposure
Crouss et al., 2018[9]	Retrospective long-term outcome study	Outcome after maintenance fluconazole	Relapse was common after cessation; ongoing maintenance often remained necessary
Collins et al., 2020[10]	Long-term cohort of idiopathic *C. albicans* RVVC	Prognosis after suppression	Fluconazole was highly suppressive but rarely curative;
			relapse after discontinuation was frequent
Spitzer and Wiederhold, 2018[19]	Laboratory study of vaginal isolates	Susceptibility at acidic vaginal pH	Azole activity was reduced at vaginal pH in some isolates
Sobel and Akins, 2022[20]	Clinical-laboratory investigation	Susceptibility-testing conditions	Acidic-pH testing may reveal reduced activity not detected using conventional conditions
Sobel et al., 2023[18]	Longitudinal resistance study	Stability of fluconazole resistance	Resistance generally persisted once established; reversal was uncommon
Swidsinski et al., 2019[21]	Human vaginal biopsy study	Histopathology and biofilm	Lesions were invasive and polymicrobial and did not resemble classical biofilms
Roudbarmohammadi et al., 2016[22]	Cross-sectional microbiological study	*ALS1/ALS3* expression and biofilm	Adhesion-gene expression and biofilm formation correlated with fluconazole resistance
Mohammadi et al., 2021[23]	Clinical-isolate molecular study	Biofilm genes and susceptibility	Biofilm formation and virulence genes were common; azole resistance occurred in both *C. albicans*

			and non-*albicans* isolates
Martens et al., 2022[25]	Phase III randomized trial	Oteseconazole	Effective treatment of the presenting episode and prevention of recurrence
Sobel et al., 2022[26]	Two phase III randomized trials	Oteseconazole maintenance	Marked reduction in culture-verified recurrence through week 48
Goje et al., 2025[27]	Phase III randomized trial	Monthly ibrexafungerp	More participants remained free from mycologically proven recurrence than with placebo
Sasi et al., 2025[28]	Retrospective resistant-isolate series	Fluconazole-resistant *C. albicans*	Highlighted need for susceptibility-guided individualized treatment

Maintenance Fluconazole and Sustained Response

The best-established treatment strategy for recurrent *C. albicans* vulvovaginal candidiasis is adequate induction followed by weekly fluconazole maintenance.

In the randomized trial by Sobel et al., women received three induction doses of fluconazole before being randomized to weekly fluconazole or placebo for six months. Disease-free rates were substantially higher with active maintenance at six months. However, protection declined after treatment cessation, and less than half of the fluconazole group remained disease-free at 12 months.[8]

Long-term observational studies produced similar conclusions. Crouss et al. found that relapse was common following completion of a maintenance course and that continued or restarted suppressive treatment was frequently required.[9] Collins et al. reported that most women benefited while receiving maintenance fluconazole, but 80.9% of surveyed respondents described relapse after discontinuing weekly therapy.[10]

These findings indicate that response must be defined carefully. A patient may achieve:

- successful suppression during therapy;
- clinical cure of the presenting episode;
- mycological eradication;
- sustained remission after treatment withdrawal; or
- long-term cure.

These outcomes are not interchangeable. Maintenance fluconazole has strong evidence for suppression but substantially weaker evidence for permanent cure.

Predictive Importance of Induction Response

The maintenance trials enrolled women whose presenting episodes had responded to induction therapy. This design supports the clinical importance of controlling active infection before initiating maintenance.

Failure to achieve clinical or mycological improvement during induction should prompt assessment of:

- adherence;
- species identity;
- susceptibility;
- drug absorption or interaction;
- mixed vaginitis;
- ongoing antibacterial exposure; and
- alternative diagnoses.

Beginning maintenance without adequately treating the presenting episode may allow persistent organisms and inflammation to continue.

Infecting Species as a Predictor

Candida albicans

Most women with recurrent vulvovaginal candidiasis have *C. albicans* infection. Susceptible *C. albicans* generally responds to appropriate azole induction and maintenance. Nevertheless, recurrence commonly returns after suppression is stopped, indicating that organism susceptibility is not the only determinant of long-term outcome.

Host-pathogen interaction, local mucosal immunity, reinoculation, persistent colonization, and incomplete eradication may contribute to recurrence even when conventional susceptibility tests demonstrate fluconazole activity.

Non-*albicans Candida*

Non-*albicans Candida* is an important predictor of reduced response to conventional short-course fluconazole. *C. glabrata* is the most clinically significant species because it frequently demonstrates reduced azole susceptibility and may be missed on microscopy because it does not characteristically form hyphae or pseudohyphae.

The CDC notes that approximately half of women with positive cultures for non-*albicans Candida* may have minimal or no symptoms. Identification of a non-*albicans* organism should therefore be interpreted with the clinical presentation, and other causes of symptoms should be excluded before repeated treatment.[4]

In women with diabetes and *C. glabrata* vulvovaginal candidiasis, Ray et al. found that 14 days of intravaginal boric acid produced a mycological cure in 21 of 33 women in the intention-to-treat analysis, compared with 10 of 35 women treated with a single dose of fluconazole.[13]

Sobel et al. reviewed women with symptomatic *C. glabrata* vaginitis treated with boric acid or topical flucytosine. Boric acid was effective in a substantial proportion, while topical flucytosine administered nightly for 14 days achieved a successful outcome in 27 of 30 women whose disease had failed to respond to boric acid and azoles.[12]

Powell et al. also demonstrated that non-*albicans Candida* can respond to treatment when therapy is individualized according to species, previous treatment, and clinical context.[14]

The evidence supports two conclusions:

- non-*albicans Candida* predicts poorer response when conventional *C. albicans*-directed regimens are used; and
- its adverse prognostic effect can be reduced through correct species identification and targeted treatment.

Antifungal Susceptibility as a Predictor

Fluconazole-Susceptible *C. albicans*

Sobel et al. evaluated vaginal isolates from women with complicated candidal vaginitis and found that fluconazole resistance was uncommon overall.[15] This supported the continued role of fluconazole in susceptible *C. albicans* infection.

However, susceptibility results should not be interpreted without considering:

- treatment dose;
- duration;
- adherence;
- fungal burden;
- vaginal pH;
- clinical diagnosis;
- recurrence after withdrawal; and
- previous azole exposure.

A susceptible isolate does not guarantee sustained cure, because recurrence may occur after successful suppression.

Fluconazole-Resistant *C. albicans*

Fluconazole-resistant *C. albicans* has become increasingly recognized in specialist vulvovaginitis practice.

Shahid and Sobel demonstrated reduced susceptibility among isolates collected from women receiving long-term fluconazole therapy.[16] Marchaim et al. subsequently reported 25 cases of fluconazole-resistant *C. albicans* vulvovaginitis over an 11-year period. Extensive previous antifungal exposure was common, suggesting that repeated azole use contributed to selection pressure.[17]

Longitudinal data indicate that once clinically important resistance develops, it may remain stable. Sobel et al. reported that fluconazole susceptibility generally remained unchanged over time and that reversal of resistance was rare despite azole avoidance.[18]

A 2025 retrospective series of women with fluconazole-resistant *C. albicans* RVVC further emphasized the need for individualized treatment based on culture and susceptibility rather than repeated empirical fluconazole.[28]

Reduced fluconazole susceptibility is therefore one of the most clinically actionable predictors of treatment failure, particularly when:

- symptoms remain compatible with candidiasis;
- culture remains positive;
- treatment was adequate;
- adherence was confirmed; and
- alternative diagnoses were excluded.

Susceptibility Testing at Vaginal pH

Conventional antifungal susceptibility testing is generally conducted at a near-neutral pH. The vaginal environment is substantially more acidic.

Spitzer and Wiederhold demonstrated that the susceptibility of vulvovaginal *Candida* isolates to azoles may decrease at physiological vaginal pH.[19] Sobel and Akins subsequently argued that acidic-pH testing may identify reduced antifungal activity not apparent under conventional testing conditions.[20]

These observations may explain some cases of clinical failure despite apparently susceptible laboratory results. However, acidic-pH-specific clinical breakpoints have not been universally validated. Such testing should therefore be regarded as an adjunct for selected refractory cases rather than a routine replacement for standardized methods.

Previous Antifungal Exposure

Previous azole exposure was one of the most consistent features among women with resistant or refractory disease.

Potential consequences of repeated empirical treatment include:

- selection of resistant *C. albicans* subpopulations;
- increased representation of non-*albicans Candida*;
- partial symptom suppression without eradication;
- treatment of non-candidal conditions;
- reduced patient confidence;
- cumulative adverse effects;
- drug interactions; and
- delay in specialist assessment.

The association between previous azole use and resistance does not establish that standard maintenance fluconazole should be avoided in appropriately selected women. Controlled maintenance is evidence-based and differs fundamentally from repeated unconfirmed or incomplete treatment.

The stewardship distinction is therefore between:

Appropriate structured suppression

- confirmed recurrent candidiasis;
- adequate induction;
- defined maintenance schedule;
- clinical review;
- culture when failure occurs; and
- documented treatment duration.

Unstructured repeated exposure

- self-diagnosis;
- repeated single-dose therapy;
- absent species identification;
- no evaluation of adherence;
- no culture during persistent symptoms; and
- no planned reassessment.

Diabetes and Metabolic Factors

Diabetes is recognized as a predisposing factor for complicated vulvovaginal candidiasis. Hyperglycaemia may:

- increase fungal adhesion;
- alter local immune responses;
- increase glucose availability in genital secretions;
- promote persistent colonization; and
- increase the likelihood of non-*albicans Candida*.

The study by Ray et al. is particularly relevant because it included women with diabetes and demonstrated that *C. glabrata* responded substantially better to boric acid than to single-dose fluconazole.[13]

This result suggests that diabetes may affect treatment response partly through changes in species distribution and antifungal susceptibility rather than through metabolic status alone.

Clinical assessment should include:

- history of diabetes;
- current glycaemic control;
- medication adherence;
- symptoms of undiagnosed hyperglycaemia; and
- evaluation for persistent metabolic risk.

Optimization of glycaemic control should accompany antifungal treatment in women with poorly controlled diabetes.

Clinical Severity and Alternative Diagnoses

Marked erythema, vulvar oedema, fissuring, excoriation, and severe pain commonly lead clinicians to prescribe longer treatment. However, clinical severity alone is not a reliable indicator of organism burden or antifungal resistance.

Persistent symptoms after treatment may represent:

- continuing candidiasis;
- residual mucosal inflammation;
- irritant or allergic contact dermatitis;
- adverse effects of topical antifungals or boric acid;
- vestibulodynia;
- vulvodynia;
- lichen sclerosus;
- lichen planus;
- desquamative inflammatory vaginitis;
- aerobic vaginitis; or
- mixed infection.

Clinical response and mycological response should therefore be reported separately.

A woman who remains symptomatic but has repeatedly negative cultures should not automatically receive escalating antifungal therapy. Conversely, a positive culture in an asymptomatic woman may represent colonization rather than active disease.

The CDC recommends culture or polymerase-chain-reaction testing in complicated vulvovaginal candidiasis and advises clinicians to identify non-*albicans Candida* and consider susceptibility testing in women who remain culture-positive despite maintenance therapy.[4]

Histopathological Predictors

Histopathological evidence in human vulvovaginal candidiasis remains limited because biopsy is not routinely required and may be inappropriate for uncomplicated disease. Swidsinski et al. examined vaginal biopsies from women with clinically, microscopically, and culture-confirmed vulvovaginal candidiasis. The lesions demonstrated fungal invasion and polymicrobial involvement but did not exhibit the classical surface biofilm architecture often described in laboratory models.[21]

The study has several implications.

First, epithelial invasion may be relevant to symptom severity and persistence. Second, bacteria and fungi may interact within vulvovaginal lesions. Third, in-vitro biofilm formation should not automatically be interpreted as evidence that mature surface biofilms are the dominant pathological mechanism in patients.

The clinical prognostic significance of the following findings remains uncertain:

- depth of fungal invasion;
- epithelial disruption;
- neutrophilic density;
- polymicrobial co-invasion;
- epithelial barrier markers; and
- tissue-associated fungal burden.

Histopathological examination may be useful in selected women with persistent vulvar lesions, ulceration, treatment-refractory inflammation, or suspected dermatosis, but it is not routinely indicated solely to confirm recurrent candidiasis.

Biofilm Formation and Virulence Factors

Biofilm formation has been proposed as a mechanism of antifungal tolerance and recurrence. Biofilm-associated organisms may show:

- altered metabolic activity;
- reduced drug penetration;
- extracellular matrix production;
- increased expression of efflux pumps;
- enhanced adhesion;
- increased stress tolerance; and
- persistence despite antifungal exposure.

Roudbarmohammadi et al. evaluated *ALS1* and *ALS3* expression in vaginal *C. albicans* isolates. Expression of these adhesion-associated genes was common and was associated with greater adherence, biofilm formation, and fluconazole resistance.[22]

Mohammadi et al. reported biofilm formation in 54.3% of vaginal *Candida* isolates. Fluconazole resistance was detected in both *C. albicans* and *C. glabrata*, and virulence genes including *ALS1*, *ALS3*, and *HWP1* were frequently identified.[23]

These findings support an association between biofilm-related phenotypes and reduced laboratory susceptibility. However, most studies were cross-sectional and did not prospectively correlate biofilm measurements with standardized patient-level treatment outcomes.

Biofilm formation should therefore be considered:

- a plausible marker of microbial persistence;
- a correlate of reduced susceptibility in some isolates; and
- a research predictor requiring further clinical validation.

It should not yet be used independently to determine treatment in routine practice.

Mycological Clearance

Mycological eradication after induction is a clinically useful marker, particularly before prolonged maintenance therapy.

Failure to clear the organism may indicate:

- resistant or less-susceptible species;
- inadequate treatment duration;
- non-adherence;
- persistent high fungal burden;
- reinoculation;
- poor absorption;
- interacting medication;
- incorrect administration of topical treatment; or
- laboratory or diagnostic uncertainty.

Clinical cure without mycological cure may be followed by early relapse. Conversely, persistent symptoms with negative cultures suggest inflammation, mixed pathology, or an alternative diagnosis.

Routine test-of-cure culture is not required for every uncomplicated episode. It becomes more relevant when:

- the disease is recurrent;
- the organism is non-*albicans*;
- treatment has failed;
- resistance is suspected;
- symptoms recur during maintenance; or
- a major change in therapy is being considered.

Adherence as a Predictor

Adherence is central to treatment response but is inconsistently measured in the literature.

Maintenance regimens may fail because women:

- discontinue medication after early symptom relief;
- misunderstand the suppressive purpose of treatment;
- forget weekly doses;
- experience gastrointestinal or local adverse effects;
- fear prolonged medication use;
- encounter cost or availability barriers;
- receive conflicting advice; or
- are not given a clear follow-up plan.

Long-term outcome studies demonstrate that women often require extended suppression beyond an initial six-month course.[9,10] A treatment should not be classified as microbiologically ineffective until adherence, dosing, administration, and duration have been reviewed.

Stewardship interventions should include:

- written dosing instructions;
- expected duration;
- explanation of induction and maintenance phases;
- management of missed doses;
- adverse-effect counselling;
- review of pregnancy potential;
- assessment of interactions;
- and planned reassessment.

Alternative Therapy for Non-*albicans* and Resistant Disease

Boric Acid

Boric acid has the strongest published clinical evidence among non-azole treatments for *C. glabrata* vulvovaginal candidiasis.

In the Ray et al. study, boric acid was superior to single-dose fluconazole for mycological cure in diabetic women with *C. glabrata*.[13]

Guaschino et al. compared topical boric acid with oral itraconazole as maintenance therapy for recurrent vulvovaginal candidiasis. Culture positivity and signs and symptoms during treatment were broadly similar between groups.[11]

Boric acid requires careful counselling because:

- it is toxic if ingested orally;
- it should be stored away from children;
- local irritation may occur;
- it should not be used during pregnancy;
- and compounding quality may vary.

Topical Flucytosine

Topical flucytosine was successful in 90% of a small series of women with *C. glabrata* vaginitis who had failed boric acid and azole therapy.[12]

The evidence remains limited by:

- retrospective design;
- small sample size;
- specialist-centre selection;
- limited availability;
- and the need for compounding.

Nevertheless, it represents an important option in specialist management of refractory *C. glabrata*.

Topical Maintenance

Expert consensus supports intermittent topical azoles, nystatin, or boric acid when oral maintenance is contraindicated, not tolerated, or inappropriate. Species identification and previous response should guide selection.[29]

Novel Antifungal Agents

Oteseconazole

Oteseconazole is a selective fungal CYP51 inhibitor developed to reduce off-target human cytochrome-P450 effects while providing prolonged antifungal activity.

The phase III study by Martens et al. found oteseconazole effective for treatment of the presenting acute episode and prevention of subsequent recurrence in women with recurrent disease.[25]

In the two VIOLET trials, women whose screening episode responded to fluconazole induction were randomized to oteseconazole or placebo. Culture-verified recurrence through week 48 occurred in approximately 5% of oteseconazole-treated participants compared with about 40% of participants receiving placebo.[26]

Oteseconazole is approved in the United States to reduce the incidence of RVVC in females who are not of reproductive potential. Its reproductive restrictions, long persistence, approved indication, and local availability must be considered before treatment.

Ibrexafungerp

Ibrexafungerp is an orally active triterpenoid antifungal that inhibits β-(1,3)-D-glucan synthase and therefore acts through a non-azole mechanism.

In the phase III CANDLE trial, monthly ibrexafungerp was compared with placebo following initial treatment. At the test-of-cure assessment, 70.8% of participants receiving ibrexafungerp and 58.5% receiving placebo remained free of mycologically proven recurrence.[27]

The non-azole mechanism may be useful for women with:

- azole intolerance;
- clinically significant interactions;
- concerns about cumulative azole exposure; or
- selected resistant isolates.

However, its use should remain microbiologically and clinically justified.

Antifungal Stewardship

Direct Evidence

No controlled trial identified in this review directly evaluated a comprehensive antifungal-stewardship programme specifically for recurrent vulvovaginal candidiasis.

The impact of stewardship must therefore be inferred from evidence supporting its individual components:

- diagnostic confirmation;
- species identification;
- susceptibility testing in refractory cases;
- adequate induction;

- structured maintenance;
- adherence assessment;
- alternative-diagnosis review;
- and avoidance of repeated unconfirmed treatment.

It would be inappropriate to assign a numerical effect to stewardship based on the current literature.

Diagnostic Stewardship

Diagnostic stewardship begins by confirming that candidiasis is responsible for the patient's symptoms.

A practical diagnostic sequence includes:

- detailed symptom and treatment history;
- vulvar and vaginal examination;
- vaginal pH assessment where appropriate;
- microscopy;
- fungal culture in recurrent or complicated disease;
- species identification;
- and investigation for alternative or mixed diagnoses.

Positive culture alone is insufficient when symptoms are absent or inconsistent with candidiasis. Conversely, negative microscopy does not exclude *C. glabrata*.

Species-Level Stewardship

Species identification influences therapy because:

- *C. albicans* usually responds to azoles;
- *C. glabrata* may require prolonged or alternative therapy;
- *C. krusei* is intrinsically resistant to fluconazole;
- and uncommon species may show distinct susceptibility patterns.

Repeated fluconazole should not be prescribed indefinitely without species confirmation in women with persistent culture-positive disease.

Susceptibility Stewardship

Susceptibility testing should be considered when:

- culture remains positive after adequate therapy;
- symptoms recur during maintenance;
- *C. albicans* resistance is suspected;
- a non-*albicans* species is identified;
- or previous azole exposure is extensive.

Testing should complement rather than replace clinical assessment.

Treatment Stewardship

Treatment stewardship requires:

- an adequate induction phase;
- therapy appropriate to species;
- appropriate dose and duration;
- avoidance of repeated single-dose treatment for complicated disease;
- a documented maintenance plan;
- monitoring for adverse effects and interactions;
- and reassessment when expected response is not achieved.

Follow-Up Stewardship

Every prolonged regimen should include:

- a clinical review date;
- a treatment stop or reassessment date;
- instructions for recurrent symptoms;
- criteria for repeat culture;
- and a plan for referral when disease remains refractory.

Table 2. Proposed Antifungal-Stewardship Framework

Stewardship step	Recommended action	Intended benefit
Confirm symptomatic infection	Examination, microscopy and culture in recurrent disease	Avoid treatment of colonization and alternative diagnoses
Identify the organism	Species-level identification	Detect non-*albicans Candida* and intrinsically less-susceptible species
Review previous exposure	Document prescribed and over-the-counter antifungals	Identify selection pressure and inadequate prior therapy
Use adequate induction	Treat active disease before maintenance	Improve initial clinical and mycological control
Assess adherence	Review dosing, duration and administration	Distinguish non-adherence from microbiological failure
Test susceptibility selectively	Test persistent culture-positive or refractory isolates	Guide treatment of resistant infection
Individualize therapy	Match regimen to species, susceptibility, safety and prior response	Increase appropriate treatment
Reconsider the diagnosis	Investigate persistent culture-negative symptoms	Prevent unnecessary escalation
Establish follow-up	Document review and stop dates	Reduce indefinite unsupervised exposure
Monitor outcomes	Record clinical and mycological response separately	Improve interpretation of treatment success

Clinicopathological and Microbiological Predictor Summary

Table 3. Predictors of Treatment Response

Predictor	Association with response	Strength and limitations of evidence
Fluconazole-resistant *C. albicans*	Strongly predicts failure of fluconazole	Supported by resistant-isolate series and longitudinal studies
Non-*albicans Candida*	Reduced response to conventional fluconazole	Consistent clinical evidence; modified by targeted therapy
C. glabrata	Poor response to single-dose fluconazole	Comparative and retrospective evidence supports alternatives
Previous repeated azole exposure	Associated with resistant and refractory disease	Strong biological plausibility; mainly observational evidence

Adequate induction response	Favourable prognostic marker before maintenance	Supported indirectly by maintenance-trial designs
Maintenance adherence	Improves suppression during therapy	Clinically important but inconsistently measured
Mycological clearance	Likely reduces early recurrence	Outcome definitions and testing schedules vary
Diabetes and poor glycaemic control	May reduce response and increase non-*albicans* infection	Evidence partly confounded by species distribution
Heavy fungal burden	Plausible predictor of slower eradication	Limited standardized prospective data
Biofilm-forming phenotype	Associated with laboratory antifungal resistance	Clinical predictive validity remains uncertain
Adhesion and virulence genes	Correlate with biofilm and reduced susceptibility	Cross-sectional microbiological evidence
Epithelial invasion	May contribute to severe or persistent inflammation	Few human tissue studies; prognostic significance unknown
Mixed or alternative vaginitis	Predicts persistent symptoms despite antifungal treatment	Strong clinical rationale; limited standardized outcome studies
Oteseconazole maintenance	Substantially reduces recurrence in eligible women	High-quality phase III evidence
Monthly ibrexafungerp	Reduces mycologically proven recurrence	Phase III evidence; long-term comparative data remain limited

Discussion

Principal Findings

This systematic review demonstrates that the strongest predictors of treatment response in recurrent vulvovaginal candidiasis are microbiological and treatment related.

Reduced fluconazole susceptibility and non-*albicans Candida* consistently predict poor response to conventional fluconazole. Repeated previous azole exposure is frequently present among women with resistant *C. albicans*. Conversely, adequate induction, microbiological control, species-directed treatment, and adherence-supported maintenance favour successful suppression.

Clinical and pathological predictors are less well validated. Diabetes, high fungal burden, marked inflammation, epithelial invasion, and biofilm-associated phenotypes are biologically plausible, but studies have not used standardized definitions or sufficiently consistent clinical outcomes.

Suppression Versus Cure

A central finding is the distinction between suppression and cure.

Weekly fluconazole prevents recurrence in most women during active treatment, but many relapse after cessation.[8-10] The recurrence does not necessarily mean that treatment was initially inappropriate. It may reflect persistence of the underlying predisposition to symptomatic mucosal disease.

Patients should be counselled that:

- maintenance therapy usually controls recurrence;
- complete long-term cure is not guaranteed;
- relapse after withdrawal is common;
- and some women require individualized longer-term suppression.

This counselling may improve adherence and reduce disappointment or inappropriate self-escalation.

Resistance Must Be Confirmed, Not Assumed

Resistance is clinically important but should not be assumed solely because symptoms persist.

Persistent symptoms may arise from:

- non-adherence;
- insufficient induction;
- incorrect diagnosis;
- mixed vaginitis;
- contact irritation;
- or post-infectious vulvar pain.

Resistance becomes more likely when symptoms remain compatible with candidiasis and repeated cultures yield the same organism despite adequate treatment.

Species Identification Changes Prognosis

The adverse prognostic effect of non-*albicans Candida* is partly treatment dependent. *C. glabrata* predicts poor response when single-dose fluconazole is used, but outcomes improve when boric acid, topical flucytosine, or other species-appropriate regimens are selected.

Species should therefore be viewed as both:

- a prognostic marker; and
- a treatment-selection marker.

Biofilm Findings Require Caution

Biofilm formation is frequently linked with antifungal resistance in laboratory studies. Nevertheless, the human biopsy evidence does not support a simple model in which recurrent vulvovaginal candidiasis is universally maintained by a classical vaginal-surface biofilm.

The discrepancy between laboratory and tissue findings may reflect:

- differences between in-vitro surfaces and human epithelium;
- transient or microscopic biofilm structures;
- strain selection;
- polymicrobial interactions;
- and the possibility that adhesion and invasion are more important than mature biofilm architecture.

Biofilm assays are not currently ready for routine clinical prediction.

Stewardship Is More Than Restriction

Antifungal stewardship should not be interpreted as withholding treatment from women with well-documented recurrent candidiasis.

Appropriate stewardship may increase antifungal use in some patients by ensuring that they receive:

- adequate induction;

- sufficient maintenance;
- species-directed alternatives;
- or susceptibility-guided therapy.

At the same time, it reduces inappropriate treatment in women with:

- negative cultures;
- colonization without symptoms;
- dermatitis;
- vulvodynia;
- or mixed non-candidal disease.

The goal is not minimum antifungal consumption. The goal is optimal, evidence-based antifungal use.

Proposed Clinical Pathway

Initial Assessment

Document:

- number of episodes;
- previous positive cultures;
- previous species;
- all prescription and non-prescription treatments;
- adherence;
- antibacterial use;
- diabetes;
- immune status;
- pregnancy potential;
- and drug interactions.

Confirm Active Disease

Perform examination, microscopy, and culture during symptoms.

Identify Species

Obtain species-level identification for recurrent, complicated, severe, or refractory disease.

Treat the Presenting Episode

Use an adequate induction regimen appropriate to severity and species.

Begin Maintenance When Appropriate

Use evidence-based maintenance after satisfactory control of the presenting episode.

Investigate Treatment Failure

Review:

- adherence;
- repeat culture;
- species;
- susceptibility;
- alternative diagnoses;
- mixed infection;
- and metabolic factors.

Refer Refractory Disease

Specialist referral should be considered for:

- fluconazole-resistant *C. albicans*;
- persistent *C. glabrata*;
- uncommon species;
- culture-negative persistent symptoms;
- suspected vulvar dermatosis;
- or need for compounded therapy.

Strengths

This review has several strengths.

- It integrates treatment trials, long-term follow-up studies, antifungal-resistance investigations, non-*albicans Candida* treatment studies, molecular virulence studies, and human histopathology.
- It distinguishes clinical response, mycological response, suppression, recurrence, and long-term cure.
- It also separates established clinical predictors from laboratory findings that remain investigational.

Limitations

The review has important limitations.

- First, definitions of recurrent vulvovaginal candidiasis varied between studies. Some required three episodes per year, while others required four.
- Second, diagnostic confirmation was inconsistent. Some studies required microscopy and culture, whereas others relied on specialist clinical diagnosis or historical positive cultures.
- Third, outcome definitions varied substantially. Clinical cure, mycological cure, recurrence, and sustained remission were assessed at different times.
- Fourth, susceptibility-testing methods and interpretive criteria changed over time and were not uniform across studies.
- Fifth, many studies were retrospective and originated from specialist referral centres. These populations may contain a disproportionate number of women with resistant organisms, non-*albicans Candida*, prolonged previous treatment, and complex alternative diagnoses.
- Sixth, histopathological and biofilm studies were generally small and did not consistently report prospective treatment outcomes.
- Seventh, no controlled study directly evaluated a formal antifungal-stewardship intervention in recurrent vulvovaginal candidiasis. Stewardship recommendations are therefore based on evidence for individual diagnostic and treatment components rather than a proven bundled-programme effect.
- Finally, a quantitative meta-analysis was not performed because clinical and methodological heterogeneity would have limited the validity of pooled estimates.

Future Research

Future studies should adopt standardized definitions and outcome measures.

Priority areas include:

- prospective validation of treatment-response predictors;
- standardized definitions of clinical and mycological cure;
- standardized follow-up after maintenance withdrawal;
- prospective studies of glycaemic control and response;
- clinical validation of susceptibility testing at vaginal pH;
- correlation of biofilm phenotypes with patient outcomes;
- non-invasive markers of epithelial invasion;
- comparative trials of treatment for azole-resistant *C. albicans*;
- comparative treatment of *C. glabrata*;

- head-to-head studies of fluconazole, oteseconazole, and ibrexafungerp in eligible populations;
- evaluation of patient-reported quality of life;
- prospective assessment of adherence;
- and randomized or stepped-wedge evaluation of antifungal-stewardship pathways.

A future stewardship trial should compare structured care with usual care and measure:

- appropriate diagnostic testing;
- antifungal exposure;
- time to correct diagnosis;
- clinical cure;
- mycological cure;
- recurrence;
- resistance;
- adverse effects;
- healthcare use;
- and patient satisfaction.

Conclusion

Recurrent vulvovaginal candidiasis is a heterogeneous disorder whose treatment response cannot be predicted from symptoms alone.

The most important adverse predictors are:

- fluconazole-resistant *C. albicans*;
- non-*albicans Candida*, particularly *C. glabrata*;
- repeated previous azole exposure;
- incomplete or inappropriate treatment;
- poor adherence;
- and failure to reconsider alternative diagnoses.

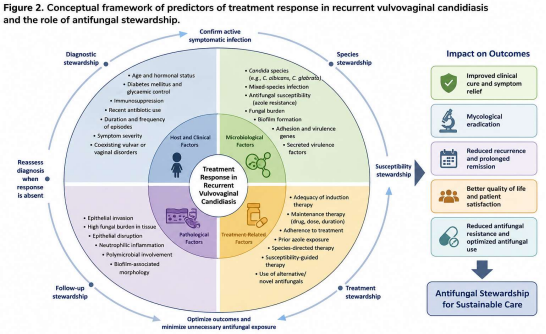
Diabetes, high fungal burden, severe inflammation, epithelial invasion, and biofilm-related virulence may also influence outcome, although their independent predictive value is less certain.

Maintenance fluconazole provides effective suppression for susceptible *C. albicans* disease but is rarely permanently curative. Species-directed treatment improves management of non-*albicans Candida*. Oteseconazole and ibrexafungerp have expanded recurrence-prevention options for appropriately selected patients.

Antifungal stewardship should ensure that symptomatic infection is confirmed, the infecting species is identified, treatment is adequate, adherence is supported, susceptibility testing is used selectively, and persistent symptoms are diagnostically reassessed.

The central stewardship principle is not simply to reduce antifungal use, but to provide the correct antifungal treatment to the correct patient for a microbiologically and clinically supported indication.

Figure 2. Conceptual framework of predictors of treatment response in recurrent vulvovaginal candidiasis and the role of antifungal stewardship.



This framework illustrates the multidimensional predictors of treatment response in recurrent vulvovaginal candidiasis and how antifungal stewardship principles integrate at every step to optimize outcomes and minimize antifungal resistance.

Declarations

Ethical Approval

Ethical approval was not required because this study was a systematic review of previously published literature.

Availability of Data and Materials

All evidence evaluated in this review was obtained from published and publicly accessible sources.

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Conflict of Interest

The authors declare no conflict of interest.

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