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Advances in Management of Vaginal Candidiasis: A Review of Modern Antifungal Therapies and Resistance Trends

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Abstract

Vulvovaginal candidiasis (VVC) is a common mucosal infection affecting up to 75% of women at least once in their lifetime, and 5–10% of women suffer from recurrent episodes (RVVC). This review provides a comprehensive overview of current and emerging therapies for VVC, focusing on modern antifungal treatments and trends in antifungal resistance. First-line therapy for uncomplicated VVC remains azole antifungals (topical imidazoles or oral fluconazole), which are effective against Candida albicans in most cases. However, rising infections with non-albicans Candida (NAC) species (e.g., Candida glabrata) pose challenges because they are less susceptible to azoles. We discuss alternative agents such as boric acid and nystatin for azole-resistant cases, as well as emerging therapeutics. Two new antifungal drugs—ibrexafungerp (a first-in-class triterpenoid) and oteseconazole (a novel azole)—have recently been approved, marking significant advances in VVC management. Clinical trials show these agents achieve high mycological cure rates, including in azole-resistant or recurrent cases. We also review adjunctive strategies, such as probiotics aimed at restoring vaginal microbiota balance, and investigational approaches, including antifungal vaccines and immunotherapies. A section on resistance mechanisms highlights how Candida species develop antifungal resistance and the global trends in resistance prevalence. **In conclusion,** while traditional azoles remain the cornerstone of therapy, emerging drugs and biological approaches promise improved outcomes for refractory and recurrent VVC. Ongoing research into combination therapies, microbiome modulation, and vaccines may further reduce the burden of this common infection.

Keywords: vulvovaginal candidiasis; antifungal therapy; azole resistance; recurrent candidiasis; non-albicans Candida; probiotics; vaginal microbiome; women's health

1. Introduction

Vulvovaginal candidiasis (VVC) is an exceedingly common infection of the lower female genital tract, primarily caused by Candida yeast overgrowth. It is estimated that roughly 70–75% of women will

experience at least one episode of VVC in their lifetime. VVC is most prevalent during reproductive ages and is a major cause of vaginitis symptoms such as pruritus, discharge, and irritation. Though not life-threatening, recurrent or chronic VVC can significantly impair quality of life and sexual health. Globally, the burden of recurrent VVC (defined as ≥3–4 episodes per year) is substantial: about 138 million women are affected annually, with an estimated global prevalence of about 7–8% among women of childbearing age. One projection suggests that by age 50, roughly 1 in 4 women will have experienced recurrent VVC. These statistics underscore the public health importance of VVC and the need for effective management strategies.

Etiology and classification: VVC is most often caused by Candida albicans, a yeast that is part of the normal vaginal microflora in many women. For reasons not fully understood, C. albicans can transition from a commensal organism to a pathogenic, invasive form in the vagina. Infection occurs when the yeast proliferates and induces an inflammatory response in vaginal tissues. VVC is typically classified as either uncomplicated or complicated. **Uncomplicated VVC** refers to sporadic, mild-to-moderate episodes—usually caused by C. albicans in immunocompetent women—that respond readily to azole therapy. **Complicated VVC** includes severe acute infections, infections by non-albicans species, occurrence in special populations (such as pregnant or diabetic women), or **recurrent VVC (RVVC)**, which is usually defined as ≥3–4 episodes in one year. RVVC represents a therapeutic challenge and often necessitates maintenance therapy or novel interventions.

Risk factors: A variety of host and environmental factors can predispose women to VVC. Elevated estrogen levels (e.g., during pregnancy or with estrogen-based contraception) and recent antibiotic use are well-known risk factors that disrupt the normal vaginal flora (notably lactobacilli) and promote yeast overgrowth. Other factors associated with VVC or RVVC include poorly controlled diabetes mellitus, immunosuppressive therapy, and genetic or immunologic factors that affect mucosal immunity. Behavioral factors (like frequent sexual activity or use of intrauterine devices) may also contribute in some cases. However, many women with recurrent yeast infections have no identifiable predisposing condition ("idiopathic" RVVC). Recent immunological studies suggest that recurrent VVC may be related more to an aberrant innate immune response (e.g., hyper-reactive neutrophils causing inflammation) than to systemic immunodeficiency. Unlike invasive candidiasis, VVC occurs in otherwise healthy, immunocompetent women, indicating that local mucosal factors are paramount.

Clinical presentation: VVC classically presents with vulvovaginal itching, burning, and a vaginal discharge that is often described as white and curd-like (though discharge may be minimal or thin in many cases). Other symptoms include vulvar redness, swelling, and dysuria or dyspareunia due to tissue irritation. The intensity of symptoms can range from mild to very distressing, especially in severe or recurrent cases. Notably, infections caused by C. albicans tend to produce robust inflammation and symptoms, whereas those caused by certain non-albicans species (like C. glabrata) may have a more subtle presentation (with less discharge or erythema). This can sometimes delay diagnosis, as mild symptoms might be attributed to other causes.

Diagnosis: The diagnosis of VVC is confirmed by demonstrating Candida organisms in vaginal secretions, either via microscopy or culture. On pelvic examination, vulvar erythema and edema may be noted, and a sample of discharge can be examined. Microscopic visualization of yeast (budding yeasts or

pseudohyphae) on a saline or KOH wet mount supports the diagnosis. If microscopy is negative but clinical suspicion is high (e.g., in recurrent cases or treatment failures), a vaginal culture or PCR test is recommended to identify the Candida species and potential antifungal susceptibilities. Identification of the species is clinically relevant because non-albicans species (which cause a minority of VVC cases) may require different management.

Candida Species and Resistance Trends

Although Candida albicans remains the leading cause of VVC in most settings, the epidemiology of causative species is shifting. Historically, C. albicans accounted for over 85–90% of VVC cases. It still dominates overall, especially in acute infections, but **non-albicans Candida (NAC) species** are responsible for a significant minority of infections, particularly in recurrent or chronic cases. Common NAC species in VVC include Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei (also known by newer taxonomic names in some cases). Epidemiologic studies report that NAC species account for about 10% to 25% of VVC cases, with higher proportions in subsets of patients with RVVC or prior azole exposure. For example, a 2020 laboratory-based study of women with RVVC reported non-albicans yeasts in 24.4% of cases, with C. glabrata being the most common NAC isolate. Similarly, clinic-based data indicate that NAC species tend to be overrepresented in patients who have failed standard azole therapy, suggesting that prior antifungal use may select for inherently less susceptible species.

The rise of NAC species is clinically significant because these organisms often exhibit **reduced susceptibility or resistance to azole antifungals**. Candida glabrata, in particular, has emerged as a frequent cause of azole-refractory VVC. C. glabrata is typically less sensitive to fluconazole than C. albicans, with many strains being dose-dependent susceptible or outright resistant to fluconazole (and to other azoles in some cases). Candida krusei is intrinsically resistant to fluconazole as well, though it is a less common cause of vaginitis. The increasing isolation of C. glabrata in VVC correlates with widespread azole usage; over-the-counter use of azole creams may create selective pressure favoring these resistant yeasts. Additionally, prolonged suppressive therapy in RVVC can lead to acquired resistance in initially susceptible strains of C. albicans, though this appears relatively infrequent (one study found ~7% of patients on long-term fluconazole developed secondary resistance).

Mechanistically, azole resistance in Candida often involves mutations in the ERG11 gene (which encodes the azole target enzyme) or upregulation of efflux pumps that expel the drug from fungal cells. These resistance mechanisms have been well documented in C. albicans and NAC species from recurrent or persistent VVC cases. Clinically, standard azole therapy may fail against resistant strains, necessitating alternative treatments. Indeed, **fluconazole-resistant VVC** is a growing concern. Fluconazole resistance rates in vaginal Candida isolates remain relatively low overall (e.g., <5% of C. albicans isolates show high-level resistance), but most C. glabrata isolates show reduced azole susceptibility. Moreover, the presence of NAC species can predict fluconazole treatment failure, even without formal resistance testing.

To illustrate species distribution and its relevance to therapy, **Figure 1** shows an estimated breakdown of Candida species in recurrent VVC and highlights those associated with azole resistance. C. albicans remains the predominant pathogen, but the proportional presence of C. glabrata and other NAC species is considerable in recurrent cases.

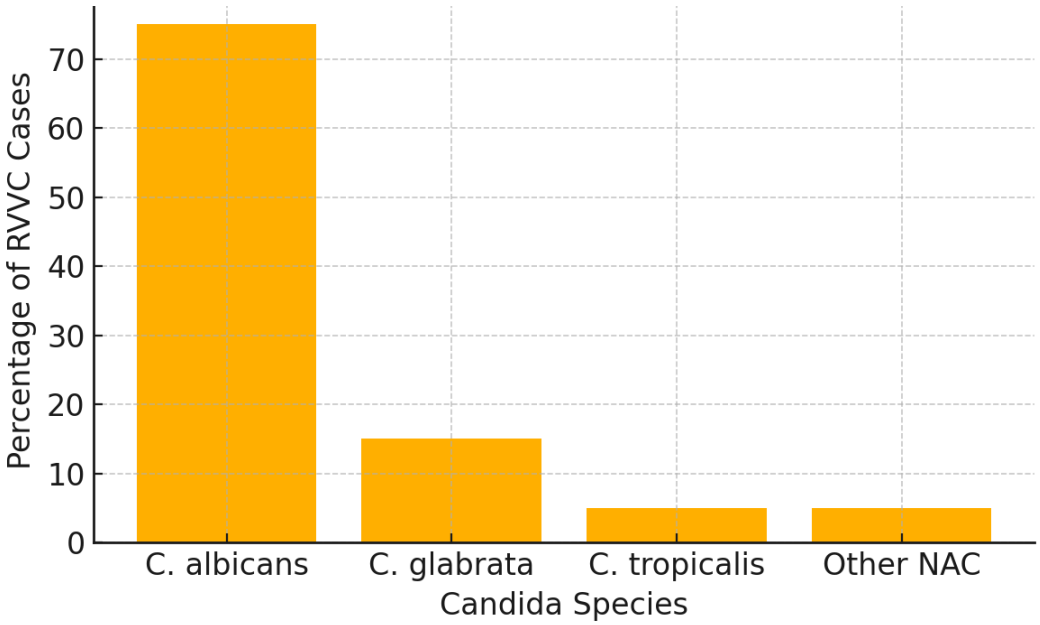


Figure 1: Estimated species distribution in recurrent vulvovaginal candidiasis. Candida albicans causes most VVC cases, while non-albicans species (notably C. glabrata and C. krusei, among others) account for a significant minority. Non-albicans Candida (NAC) species tend to have higher rates of azole resistance, complicating treatment. (Data synthesized from global reviews of RVVC epidemiology.)

Another emerging pathogen in the Candida family is Candida auris, known for multidrug resistance; however, it is primarily associated with invasive infections in hospital settings and has only rarely been implicated in vaginal infections. For VVC, the main concerns remain C. glabrata and other NAC yeasts that challenge our current antifungal arsenal.

In summary, VVC resistance trends are characterized by a shifting **pathogen spectrum and increasing antifungal resistance**. Clinicians now more often encounter VVC cases that do not respond to fluconazole, either because of infection with a resistant NAC species or, less commonly, a resistant strain of C. albicans. This trend underscores the importance of proper species identification and susceptibility consideration in recurrent or refractory cases. It also fuels the demand for new treatment options beyond the conventional azole drugs.

Traditional Antifungal Therapies for VVC

Management of acute VVC has long relied on azole antifungals, which target the ergosterol synthesis pathway in Candida. The azoles can be delivered topically or orally and have proven highly effective for uncomplicated VVC. **Current guidelines** (such as the CDC and IDSA guidelines) recommend either a short-course topical azole or a single dose of oral fluconazole as first-line therapy for uncomplicated VVC. Patient preference, cost, and convenience often guide the choice between topical and oral therapy, as cure rates are roughly equivalent (around 80–90% initial clinical response for uncomplicated cases) regardless of route. Below is an overview of the standard therapies:

- **Topical azoles:** A variety of imidazole antifungal creams and suppositories are available over-the-counter, including clotrimazole, miconazole, tioconazole, and others. Typical regimens range from

single high-dose applications (e.g., tioconazole 6.5% ointment, one day) to 3-day or 7-day courses of creams or ovules (e.g., miconazole 2% cream for 7 nights, or 1200 mg vaginal suppository once). These medications provide high local antifungal concentrations, are generally well tolerated (though local burning or irritation can occur), and avoid systemic side effects. No single topical azole has shown clear superiority, and cure rates are comparable across azole formulations. Topical azoles are effective for most C. albicans infections and can also be used in mild NAC infections, though treatment failure is more likely if the strain has reduced azole susceptibility.

- **Oral fluconazole:** Fluconazole is a triazole antifungal that revolutionized VVC treatment with its one-dose oral regimen. A 150 mg oral dose of fluconazole achieves clinical and mycologic cure in a large proportion of acute VVC cases and is convenient for patients. This single-dose therapy has become a standard approach for uncomplicated VVC. It is generally safe, with mild transient side effects (such as headache or gastrointestinal upset) in a minority of patients. Fluconazole's ease of use makes it very popular, although it should be avoided in pregnancy (topical azoles are preferred for pregnant women). Importantly, fluconazole has limited efficacy against certain NAC species: for example, it is not effective against C. krusei (intrinsically resistant) and often insufficient for C. glabrata. If C. glabrata is identified, higher doses or alternative treatments are indicated (see below). Fluconazole is available by prescription in most regions, whereas topical azoles may be OTC.

- **Nystatin:** Nystatin is an older polyene antifungal that can be used intravaginally (100,000-unit suppositories) daily for 14 days. It is less commonly used now, because azoles are more convenient and often more effective against C. albicans. However, nystatin has a role in azole-resistant cases and is notably safe in pregnancy (it is not absorbed systemically). Cure rates with nystatin for acute VVC are somewhat lower than with azoles in comparative trials, but it can eradicate susceptible Candida strains and may be effective for some NAC infections. Some guidelines consider nystatin a second-line or alternative therapy, especially for patients who cannot tolerate azoles.

- **Boric acid:** Boric acid is not a classical antifungal drug but a weak acid with antiseptic and antifungal activity. It has been used as an inexpensive home remedy for decades and is now recommended in guidelines for certain refractory cases. Boric acid 600 mg, encapsulated in a gelatin capsule and inserted vaginally once daily at bedtime for at least 14 days, is an effective therapy for VVC caused by C. glabrata and other azole-resistant strains. Studies have reported mycological cure rates around 70% for C. glabrata vaginitis with a 14-day boric acid regimen, significantly outperforming fluconazole in that context (which often yields <40% cure for C. glabrata). Boric acid is thus considered a first-line treatment for C. glabrata VVC or fluconazole-resistant VVC in many protocols. It is generally well tolerated, though it can cause vaginal irritation and is toxic if ingested orally. Boric acid should not be used in pregnant women. After acute treatment, some practitioners use boric acid (e.g., twice weekly) for maintenance in recurrent cases, though data on long-term use are limited.

- **Combination topical therapy (Flucytosine + Amphotericin B):** For the most recalcitrant infections (e.g., C. glabrata that failed boric acid), compounding pharmacies can create a topical 17% flucytosine cream often combined with 3% amphotericin B cream. Applied vaginally for 14

days, this combination can eradicate even highly resistant yeasts in some cases. This regimen is relatively cumbersome and costly, reserved for salvage therapy. Some case series demonstrate success of ~70–90% in otherwise untreatable cases when using flucytosine ± amphotericin vaginal suppositories. Side effects can include irritation or ulceration, and flucytosine systemic absorption is minimal but possible (so caution in pregnancy and monitoring blood counts if used extensively).

Table 1 summarizes key traditional and modern antifungal therapies for VVC, including their routes and typical uses.

Table 1: Summary of Antifungal Therapies for Vulvovaginal Candidiasis

Therapy	Class/Type	Route & Regimen	Notable Uses & Points
Topical azoles (e.g., clotrimazole, miconazole, tioconazole, butoconazole, terconazole)	Imidazole antifungals	Vaginal cream or suppositories for 1–7 days (varies by formulation)	First-line for uncomplicated VVC; high local efficacy against C. albicans; available OTC (for many preparations); minimal systemic absorption. All topical azoles show similar cure rates.
Fluconazole (oral)	Triazole antifungal	Oral tablet, 150 mg single dose for uncomplicated VVC; for severe VVC, 150 mg every 72h × 2–3 doses. Maintenance: 150 mg weekly for 6 months (RVVC).	First-line systemic therapy; convenient one-dose treatment for acute VVC. Highly effective for azole-susceptible C. albicans, improving symptoms and quality of life. Not effective against inherently resistant species (C. krusei) and reduced efficacy for C. glabrata. Long-term suppressive therapy prevents relapses during use, but ~80% of women relapse after stopping maintenance. Contraindicated in pregnancy.
Nystatin (vaginal)	Polyene antifungal	Vaginal suppository, 100,000 units daily for 14 days	Alternative for azole-intolerant or azole-resistant cases; effective mainly for C. albicans. Safe in pregnancy (not systemically absorbed). Cure rates somewhat lower than azoles for acute VVC, but useful for azole-resistant NAC strains to some extent.
Boric Acid (vaginal)	Organic acid (antiseptic)	Vaginal capsule (suppository) 600 mg once daily for 14 days (typical); maintenance dosing (e.g.,	Recommended for VVC due to C. glabrata and other azole-resistant Candida. Achieves ~70% mycological cure in C. glabrata vaginitis, superior to fluconazole.

		twice weekly) used empirically in RVVC.	Inexpensive and accessible (can be compounded). Can cause local irritation; **not** to be used during pregnancy (teratogenic if systemic).
Flucytosine + Amphotericin B (topical compounding)	Pyrimidine analog + polyene	Compounded vaginal cream or suppository (e.g., 5-FC 17% + amphotericin B 3%) nightly for 14 days	Salvage therapy for refractory VVC (e.g., multidrug-resistant C. glabrata). Expensive and may require special compounding. Shows good success in case series when standard treatments fail. Local irritation possible.
Ibrexafungerp (Brexafemme)	Triterpenoid (glucan synthase inhibitor)	Oral tablets, 300 mg twice (total 600 mg) in one day for acute VVC; for RVVC suppression, the same 1-day regimen is given once monthly for 6 months.	**New** systemic antifungal approved 2021. First non-azole oral drug for VVC, active against C. albicans and NAC (fungicidal action). Useful for azole-resistant cases and for preventing recurrences. Trials showed ~65% of women remained infection-free during a 3-month follow-up, vs ~53% on placebo. Side effects: mostly mild GI symptoms (nausea, diarrhea). Not to be used in pregnancy (animal studies suggested fetal harm).
Oteseconazole (Vivjoa)	Novel azole (tetrazole subclass)	Oral regimen for RVVC prophylaxis: 600 mg on day 1, 450 mg on day 2, then 150 mg once weekly for 11 weeks. (An alternative regimen starts with fluconazole to treat an acute episode, followed by oteseconazole maintenance.)	**New** long-acting azole approved 2022 for preventing RVVC. Indicated only for women with recurrent VVC who are **not of reproductive potential** (e.g., postmenopausal) due to teratogenic risk. Highly potent against C. albicans and C. glabrata (up to 40× more potent than fluconazole in vitro). In phase 3 trials, ~90% of women on oteseconazole had no recurrence during a 48-week follow-up, compared to ~50% on placebo. Well tolerated; side effect profile similar to fluconazole. Represents

			a promising option for long-term suppression of RVVC.

Traditional regimen outcomes: With the above therapies, the short-term cure rate for uncomplicated VVC is generally high. Most patients experience rapid symptom relief within a few days of therapy. However, a subset of women experience **recurrent infections or persistence** despite appropriate therapy. For those with RVVC, the standard of care has been an extended "maintenance" regimen of fluconazole (150 mg weekly for 6 months) after initial clearance. Maintenance fluconazole has been shown to dramatically reduce relapse rates during the treatment period. For example, in one clinical trial, suppressive weekly fluconazole prevented recurrent infections in a majority of women while on therapy (maintenance therapy improved patients' quality of life and kept them symptom-free). However, once maintenance is stopped, VVC often returns: approximately 50–60% of women will experience a recurrence within months of discontinuing fluconazole maintenance. A 2020 follow-up study found that as many as 80% of women relapsed after stopping 6 months of fluconazole, confirming that this approach, while effective at suppressing disease, is not curative in the long term. This underscores that RVVC is a chronic condition for many, and it has fueled interest in finding better long-term solutions.

Additionally, concerns about antifungal resistance and microbiome disruption arise with long-term azole use. While fluconazole maintenance is generally safe, a small proportion of women may develop fluconazole-resistant Candida strains over time. Therefore, clinicians must balance the benefits of suppressive therapy against potential risks and advise periodic re-evaluation. If a patient on maintenance develops a breakthrough infection, or if cultures grow a less susceptible species, therapy should be adjusted (e.g., switch to boric acid or a newer agent if available).

In cases of **severe acute VVC** (extensive vulvar inflammation, fissures, edema, or ulceration), the recommendation is to use a more aggressive initial regimen: fluconazole 150 mg given in two or three sequential doses 72 hours apart (instead of a single dose), or 7–14 days of topical azole, to ensure thorough clearance of the infection. This approach has been effective in resolving intense symptoms and achieving mycologic cure in severe cases. Patients with severe VVC often experience significant symptom relief after just 24–48 hours of therapy due to reduction in yeast burden and inflammation.

- Overall, the established antifungal therapies for VVC have a strong track record, especially for uncomplicated infections caused by susceptible C. albicans. However, limitations in RVVC and azole-resistant infections have become evident. These limitations have driven **modern advances** in therapy, as discussed in the next section.

Modern and Emerging Antifungal Therapies

Significant progress in recent years has produced new treatment options for VVC, particularly for patients with recurrent or resistant infection. Here, we review major modern advances, including newly approved medications and novel strategies on the horizon.

New Antifungal Agents for VVC

Ibrexafungerp: One of the most notable recent therapies is **ibrexafungerp**, a first-in-class triterpenoid antifungal. Ibrexafungerp (brand name Brexafemme) was approved by the U.S. FDA in 2021 for VVC, becoming the first new oral antifungal for this indication in decades. It belongs to the same broad mechanism class as echinocandins (targeting β-1,3-D-glucan synthesis in fungal cell walls) but is

administered orally and is structurally distinct (a triterpenoid). Ibrexafungerp is fungicidal against Candida species and remains active in the acidic vaginal environment, where it has shown potent antifungal effects. The standard regimen is a one-day oral treatment (two doses of 300 mg given 12 hours apart). In clinical trials, ibrexafungerp showed cure rates comparable to fluconazole for acute VVC, and importantly it has efficacy against fluconazole-resistant isolates including C. glabrata. A recent Phase 3 trial (the CANDLE study) evaluated ibrexafungerp for prevention of RVVC: women who had initially been treated for VVC were given monthly ibrexafungerp or placebo for 6 months. The drug significantly reduced the risk of recurrence—about 65% of ibrexafungerp recipients remained infection-free at 6 months vs ~53% of those on placebo (a relative improvement, though not complete protection). On the basis of this, in late 2022 the FDA expanded ibrexafungerp's indication to include RVVC prophylaxis, making it the first antifungal approved to both treat acute VVC and reduce recurrence. Ibrexafungerp's safety profile includes gastrointestinal side effects (diarrhea, nausea) and it is contraindicated in pregnancy because it caused fetal harm in animal studies. Nevertheless, its oral route and broad spectrum (covering NAC species) make it a valuable addition, especially for patients with fluconazole-resistant VVC or those who cannot use azoles. It exemplifies the successful translation of an **"echinocandin-like" mechanism** into an oral agent suitable for mucosal infection.

Oteseconazole: Another breakthrough is **oteseconazole** (brand name Vivjoa), a novel azole antifungal specifically developed for RVVC. Oteseconazole is a tetrazole derivative azole that was approved in 2022 for prevention of recurrent VVC in females who are not of reproductive potential (e.g., postmenopausal women). This restriction is due to concerns about potential teratogenicity; the drug is not indicated in women who could become pregnant. Oteseconazole was designed to be more fungus-specific: it binds fungal ergosterol-synthesizing enzymes with higher affinity and has fewer off-target effects on human enzymes than fluconazole. In vitro, it is extraordinarily potent against C. albicans and many NAC species, including C. glabrata. One study reported that oteseconazole's minimum inhibitory concentrations (MICs) were on average 40-fold lower than fluconazole's against a broad panel of vaginal Candida isolates. Clinically, oteseconazole's efficacy was demonstrated in two Phase 3 trials (VIOLET and ultraVIOLET). Women with a history of RVVC received either oteseconazole or placebo after initial clearance of an acute episode (fluconazole was used to treat the acute infection, then oteseconazole was given for maintenance). The results were striking: over 90% of women receiving oteseconazole remained free of symptomatic VVC recurrences through nearly one year of follow-up, compared to roughly 40–50% of those on placebo. This corresponds to a marked reduction in recurrence risk (one trial reported a 93.5% reduction in recurrence rate relative to placebo). Oteseconazole was also non-inferior to fluconazole in treating acute episodes in these studies, meaning it can both treat and then protect against episodes. It is administered as an induction dose (typically over the first two days) followed by weekly dosing for 3 months. The side effect profile is similar to other azoles (headache, nausea in a small fraction of patients), and no serious safety signals emerged in trials aside from the reproductive toxicity in animals. Oteseconazole's approval offers a targeted solution for women with chronic yeast infections, potentially representing a **functional cure** (or long remission) for RVVC in those who are eligible to take it. Ongoing considerations include its cost and ensuring it's prescribed to the indicated population (those without childbearing potential).

Other novel agents: The antifungal pipeline includes additional agents that, while not yet approved specifically for VVC, hold promise for future use. One example is **rezafungin**, a next-generation echinocandin (long-acting) currently in development for invasive candidiasis – not directly for VVC but illustrating expanded options in antifungal therapy. There are also investigational azole derivatives (e.g.,

VT-1598, another tetrazole) which have potent activity against azole-resistant Candida strains. If these are approved for systemic use, they might be repurposed in difficult VVC cases. Likewise, **SCY-247**, a second-generation oral fungerp, is in early studies and could offer even broader spectrum activity including against emerging species like C. auris.

Notably, **echinocandins** (e.g., caspofungin, micafungin) are highly effective against Candida and there is in vitro evidence of activity against vaginal isolates, but their intravenous route limits use to rare situations of severe refractory VVC in immunocompromised patients. In general, echinocandins are not used for routine VVC because oral and topical options suffice and IV therapy is impractical for an outpatient mucosal infection.

Adjunctive and Non-Pharmacologic Therapies

Beyond antifungal drugs, there is interest in **microbiome-modulating therapies** to manage or prevent VVC. Given that lactobacilli are the dominant normal flora of the vagina and create conditions (low pH, hydrogen peroxide production) that suppress Candida, approaches that restore a healthy vaginal microbiota might help in preventing Candida overgrowth.

Probiotics: Probiotic strains (beneficial bacteria such as Lactobacillus species) have been studied as an adjunct or alternative for VVC treatment. Probiotics can be administered orally or intravaginally to reestablish a protective, lactobacillus-dominant flora. Several clinical trials and meta-analyses have examined probiotics for both acute VVC and RVVC. Overall, the findings suggest that probiotics alone are less effective than antifungal medications in clearing acute Candida infections. For instance, fluconazole or azoles cure infections at much higher rates than probiotic regimens in head-to-head comparisons. However, evidence suggests probiotics can help as an adjunct to standard antifungals and reduce recurrences. A recent comprehensive review (2024) concluded that while results have been somewhat inconsistent, many studies show that adding probiotics (e.g., Lactobacillus rhamnosus and L. reuteri strains) to azole therapy can improve short-term mycological cure and reduce the risk of relapse of VVC. Probiotic use was associated with restoration of normal vaginal pH and microbiota in these women, which likely contributes to their protective effect. For prevention, some trials of oral or vaginal probiotics in women with RVVC have shown longer infection-free intervals than placebo, though not all studies agree because strains and protocols differ. Importantly, probiotics appear safe and well tolerated, making them an attractive low-risk adjunct. Current guidelines do not universally recommend probiotics for VVC because consistent evidence is insufficient, but many clinicians consider advising them in recurrent cases given the potential benefit and minimal downside. Typical regimens include daily oral lactobacilli capsules or vaginal probiotic suppositories for several weeks. While not a cure-all, probiotics might help "reset" the vaginal ecosystem, especially after antibiotic use or in those with repeated infections.

Prebiotics and postbiotics: These are newer concepts in vaginal health. Prebiotics refer to substances that promote the growth or activity of beneficial microorganisms. In the context of VVC, a prebiotic might be a vaginal gel or suppository containing nutrients (like glycogen, peptides, or polysaccharides) that favor lactobacilli. There is limited clinical research specifically on prebiotics for VVC, but the idea is to enhance the natural defenders of the vagina so that Candida is kept in check. Postbiotics are products or metabolites from probiotic bacteria (such as lactic acid, bacteriocins, or enzymes) that can directly inhibit pathogens or modulate the host environment. A practical example is boric acid or lactate gel, which acidifies the vagina to a pH that suppresses Candida growth; one might consider this a postbiotic approach, since a key function of vaginal lactobacilli is producing lactic acid. Another potential postbiotic could be enzymes

that disrupt Candida biofilms. While these concepts are promising, they remain largely experimental. A clinical trial is currently underway testing a "postbiotic" vaginal suppository (essentially a lactobacillus ferment filtrate) as adjunctive treatment for acute VVC. The results of such studies will clarify if these strategies can join the arsenal against VVC.

Lifestyle and behavioral modifications: Patient education is an important adjunct to prevent recurrent VVC. Simple measures like avoiding douching or harsh feminine hygiene products, wearing breathable cotton underwear, and managing underlying conditions (like diabetes) can help maintain vaginal microbial balance. While these measures alone won't treat an active infection, they can reduce triggers of dysbiosis that allow Candida to flourish.

Immunotherapy and Vaccines

Given that RVVC is at least partly an immunologic problem—where the host's response to Candida is dysfunctional—immunotherapeutic approaches are an intriguing area of research. A milestone effort in this domain is developing a **vaccine against Candida**. The furthest in development is the NDV-3A vaccine, which contains a recombinant fragment of the Candida albicans Als3 surface protein (also effective against Staphylococcus aureus as a target, interestingly). A Phase 2 trial of NDV-3A in women with RVVC showed that the vaccine was safe and could elicit strong immune responses (high antibody titers to Candida). In terms of efficacy, the vaccinated group had a longer time to first recurrence than placebo, and a subset of patients appeared to be protected for up to 12 months. However, the overall reduction in recurrence rate did not reach statistical significance for the full study population, meaning the vaccine's benefit, while suggestive, was not definitive. Interestingly, exploratory analysis indicated that younger women responded better, whereas women over 40 gained less benefit. This implies that host factors (such as immune aging or hormonal status) might influence vaccine effectiveness. Despite modest results, NDV-3A provides proof-of-concept that immunization can affect the course of RVVC, and further trials or optimized vaccines could enhance this approach. No antifungal vaccines are currently commercially available, but research is ongoing. The idea is a therapeutic vaccine to prevent recurrences rather than treat acute infection; a successful vaccine could drastically improve long-term management by reinforcing immune protection against Candida.

Another immunotherapeutic angle is the use of **immune modulators or cytokine therapies** to tweak the vaginal immune environment. Since neutrophils and excessive inflammation contribute to symptomatic VVC, one could imagine therapies aimed at reducing harmful inflammation while preserving antifungal activity. So far, no specific cytokine or immune therapy has entered clinical practice for VVC. Some experimental studies in mice have tried approaches like IL-17 antibodies or complement blockers to see if they reduce immunopathology, but this is far from translation to humans. For now, the focus remains on vaccines as a means to educate the immune system to better handle Candida at the mucosal level.

Addressing Recurrent and Resistant VVC: A Multi-Pronged Approach

For women suffering from RVVC or those infected with drug-resistant strains, optimal management may involve combining several of the above strategies. For example, a patient with recurrent C. glabrata vaginitis might receive a course of boric acid for acute clearance, followed by a suppressive regimen of oteseconazole or topical boric acid, along with probiotic supplementation to restore the microbiome. If she is postmenopausal, oteseconazole is an excellent option; if she is younger and pregnancy is a consideration, then long-term fluconazole (with careful monitoring) or perhaps intermittent ibrexafungerp

could be used, coupled with behavioral measures and probiotics. This kind of **individualized therapy** is recommended by expert panels, because RVVC can vary in underlying causes from patient to patient.
Moreover, combination therapy is emerging for difficult cases. Combining a conventional antifungal with a probiotic or with an anti-biofilm agent might yield better results than monotherapy. Some studies have shown that maintenance fluconazole plus weekly probiotics led to fewer relapses than fluconazole alone over 6 months. Though more research is needed, it is plausible that a synergistic approach addressing both the pathogen and the vaginal environment will be key in hard-to-treat VVC.
Finally, **patient adherence and proper diagnosis** are fundamental. Many presumed "treatment failures" in VVC are actually due to misdiagnosis (e.g., the condition was something else like dermatitis or bacterial vaginosis) or reinfection from an untreated source. Thus, in recurrent cases, verifying that Candida is truly present (via culture) and that the symptoms are not due to another coexisting condition (like vulvar eczema or vestibulodynia) is critical. If Candida is confirmed and the species identified, tailor therapy to that species' susceptibility.

2. Conclusion

Vulvovaginal candidiasis remains one of the most common infections in women, and its management is evolving in response to emerging challenges and opportunities. For decades, azole antifungals (topical imidazoles and oral fluconazole) have been the mainstay of therapy, and they still effectively treat the majority of acute VVC cases. However, the landscape is shifting: infections caused by non-albicans species and fluconazole-resistant strains, as well as the frustrating scenario of recurrent VVC, require new solutions. In this review we highlighted several **advances in VVC management**. The approval of **ibrexafungerp** provides a much-needed alternative to azoles, with robust activity against resistant Candida and the convenience of oral dosing. The introduction of **oteseconazole** specifically for RVVC prophylaxis is another leap forward – achieving high success in preventing recurrences and offering hope for women with chronic candidiasis who previously had to rely solely on off-label fluconazole suppression. These new agents, along with better use of older therapies like boric acid and nystatin in appropriate contexts, form a more comprehensive antifungal arsenal.
At the same time, a deeper understanding of VVC resistance trends and pathogenesis is shaping management. We now recognize that C. glabrata and other NAC species are not rare in vaginal infections and often underlie cases of treatment failure. Clinicians are advised to consider species identification in recurrent VVC and to choose therapy accordingly (e.g., boric acid or a novel agent for suspected C. glabrata rather than repeated fluconazole courses). Antifungal stewardship in VVC, for instance, avoiding unnecessary prolonged azole use, may help limit further resistance development in the vaginal Candida population.
Moreover, integrative approaches that account for the **vaginal microbiome** are gaining traction. While traditional antifungals target the pathogen, adjunctive probiotics or other microbiome-friendly strategies aim to restore protective lactobacilli, potentially reducing the likelihood of Candida overgrowth. Current evidence supports using probiotics as an adjunct to antifungals to reduce short-term recurrence, although definitive guidelines await more consistent trial results. It remains an active area of research, and future recommendations may more formally incorporate microbiome management (including prebiotic or postbiotic therapies) into VVC care plans, especially for prevention.
Looking ahead, **future projections** in VVC management include the potential for **vaccination** and improved immunotherapies. The Phase 2 trial of the NDV-3A vaccine, while not a home-run,

demonstrated that immune modulation can extend the infection-free interval in RVVC patients. With further refinement, a vaccine could become a reality, offering long-term protection much like vaccines do for other recurrent infections (e.g., HPV or UTIs, conceptually). Additionally, new classes of antifungals are in development – for instance, drugs targeting fungal virulence factors or biofilm formation – which could one day be applied to VVC if they prove effective and safe.

In conclusion, vaginal candidiasis management is advancing on multiple fronts. For practicing clinicians and researchers alike, it is an exciting time as long-standing gaps (such as how to reliably prevent recurrences or treat azole-resistant cases) are beginning to be filled with evidence-based interventions. A global perspective is also important: VVC affects women worldwide, and treatment accessibility is key. The newer therapies, though effective, can be costly or not yet widely available outside certain countries. Therefore, continued efforts are needed to ensure advances in VVC management lead to equitable improvements in women's health across regions. By combining traditional antifungal wisdom with modern innovations, and monitoring resistance patterns, healthcare providers can better help women find relief from this common but impactful infection.

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