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Emerging Therapeutic Approaches in Recurrent Vaginal Candidiasis: From Azoles to Probiotics

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Abstract: *The mentioned recurrent vaginal candidiasis (RVC) is a protracted, painful, debilitating malady that millions in every part of the globe suffer from all year round, suffering in frequent attacks of Candida. Although azole antifungals were historically the pillar on which antifungal therapy was kept, there are innate disadvantages of their use that led to the discovery of alternative methods of therapy, or even a combination of them. This Review will give an important overview of the existing gaps in the management of RVC and will describe the innovative interventions in this field, such as new antifungals, immunological treatments, and probiotics, and plans for addressing the microbiome. The question is how the new methods intend to fix the drawbacks of the existing treatments and provide more reasonable, personified, and successful care for women with this problematic disorder.*

Keywords: *recurrent vaginal candidiasis*

I. INTRODUCTION

The most common complicated form of vaginitis and the most widespread type of vaginal candidiasis (largely due to Candida albicans) occur in up to 75% of all women at least once in the course of their lives (Willems et al., 2020). Of them, about 5-8% face a recurrent vaginal candidiasis (RVC) during which they have had four or more attacks in a year (Rosati et al., 2020). The disease has a significant negative impact on the quality of life, and itching, discharge, burning, and irritation are its symptoms.

In spite of the popularity of azole antifungals, including fluconazole and clotrimazole, cases of treatment failure and relapses are frequent, which indicates lapses in contemporary therapy. These deficiencies entail antifungal resistance, inefficient long-term remission, failure to kill biofilms, vaginal microbiota, and the absence of patient-specific interventions. This review focuses on current limitations and considers the emerging strategies in treatment, which include new antifungals and vaccines, probiotics, and microbiome-based therapies.

II. PATHOPHYSIOLOGY AND CHALLENGES IN RVC

The Candida-Host Interaction

C. albicans is normally a nonpathogenic commensal of the vaginal ecosystem, but it changes to pathogenic form in certain specific conditions of the host or the environment, like the usage of broad-spectrum antibiotics, high estrogen levels, or immune suppression (Faustino et al., 2025). Its pathogenicity is associated with several virulence attributes that include hyphal growth, biofilm formation, and secretion of hydrolytic enzymes. As an example, Bras et al. (2024) emphasized the specificity of secreted aspartyl proteases in the invasion of mucosa; however, their study has insufficiently considered the variability of hosts, thus making it hard to generalize. Other researchers, such as Zhong et al. (2024), proposed that *Th17-mediated* response is relevant in repelling recurrence, whereas the immunological model oversimplifies the recurrence in immunocompetent women, indicating the necessity of broader thinking, such as microbial ecology.

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Factors Contributing to Recurrence

Biofilms impede antifungal penetration, allowing fungal persistence. High estrogen levels (e.g., in oral contraceptive users) enhance Candida adhesion and hyphal transition, facilitating pathogenesis (Kumwenda et al., 2022). Genetic predispositions such as Dectin-1 or CARD9 mutations impair fungal recognition and cytokine signalling. Zhao et al. (2022) proposed that host immunity plays a limited role in RVC, yet emerging genetic studies contradict this, showing significant inter-individual variation. Additionally, recurrent use of azoles disrupts the vaginal microbiota, reducing protective *Lactobacillus* spp., promoting dysbiosis and Candida overgrowth.

Candida Resistance Mechanisms

Resistance mechanisms include efflux pump overexpression (e.g., *CDR1*, *MDR1*), ERG11 gene mutations in the ergosterol synthesis pathway, and biofilm-associated protection. While Arastehfar et al. (2020) emphasized fluconazole's efficacy, real-world resistance trends suggest growing clinical failure, particularly with non-*albicans* strains, challenging reliance on azole monotherapy.

RVC is associated with complicated host-pathogen interactions. Candida albicans may alter to become pathogenic when subjected to conditions such as antibiotic treatment, when prevailing elevated levels of estrogen or when the immune system is suppressed. There are virulence factors that include hyphal transition, biofilm formation, and enzyme secretion, which also contribute to mucosal invasion and persistence. Risk factors that can lead to recurrence can be attributed to genetic predispositions (e.g., Dectin-1 mutations), hormonal cycles, and vaginal microbiota disturbances. The resistance phenomena, such as efflux pumps, ERG11 mutations, and biofilms, lower the activity of azoles. Although certain studies minimize the role of host immunity, recent findings have indicated that it plays a great role, and hence, there is a need to have a multifactorial approach to the management of RVC.

III. CONVENTIONAL TREATMENTS: STRENGTHS AND SHORTCOMINGS

Azoles as First-line Therapy

Azole antifungals, including fluconazole, miconazole, and clotrimazole, inhibit the cytochrome P450-dependent enzyme 14α-demethylase, disrupting ergosterol synthesis, a key fungal cell membrane component. Fluconazole remains the most widely prescribed due to its oral availability, affordability, and initial high efficacy. Willems et al. (2020) demonstrated clinical success rates exceeding 90% in acute vulvovaginal candidiasis (VVC); however, in cases of recurrent infections, the cure rate dropped significantly.

The limitations are increasingly apparent. Resistance is emerging, particularly among non-*albicans* species like *Candida glabrata*, which exhibit intrinsic azole tolerance (Whaley et al., 2017). Moreover, azoles are largely ineffective against biofilms — structured communities of Candida that resist antifungal penetration. Song et al. (2022) showed that biofilm-embedded *C. albicans* had up to 1000-fold higher resistance to fluconazole. Long-term use often leads to hepatotoxicity, gastrointestinal disturbances, and, critically, dysbiosis through disruption of *Lactobacillus*-dominated vaginal microbiota. Some authors, such as Fisher et al. (2022), maintain that azoles are sufficient with maintenance therapy, yet this stance underestimates the increasing prevalence of resistant strains and biofilm-associated relapse.

Alternative Antifungals

As stated by Szymański et al. (2022), Echinocandins (e.g., caspofungin) inhibit β-glucan synthesis and are effective against azole-resistant strains, but their IV-only formulation limits outpatient use. Boric acid, though useful for resistant *C. glabrata*, carries the risk of mucosal irritation and lacks standardized dosing protocols. Nystatin, a polyene antifungal, remains an option but shows inferior efficacy compared to azoles, particularly in chronic RVC.

Azoles are still the choice treatment options for vulvovaginal candidiasis owing to their low cost and early therapeutic effect, particularly fluconazole. However, they have reduced efficacy with repeated susceptibility, increasing resistance by non-albicans Candida (e.g, C. glabrata), and low biofilm activity. The damaging effects as well as the alteration of vaginal microbiota associated with long-term azole exposure are also linked. Such alternatives as echinocandins are effective against the resistant strains, yet adverse by their sole method of administration is through IV. Boric acid and

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nystatin can also be used, but neither is very tolerable or effective. The shortcomings illustrate the importance of having more resistant and directed treatment in recurrent vaginal candidiasis.

IV. GAPS IN MODERN THERAPY

Despite decades of antifungal development, modern treatment strategies for recurrent vaginal candidiasis (RVC) remain suboptimal. Several critical therapeutic gaps persist, contributing to high relapse rates, rising resistance, and unsustainable clinical outcomes.

High Relapse Rates

While azoles such as fluconazole provide rapid symptom relief, long-term efficacy remains poor. Kuhn et al. (2023) reported recurrence in up to 50% of women within three months of treatment cessation. Although extended fluconazole prophylaxis can delay recurrence, as Sobel suggested, it often fails to prevent eventual relapse once therapy is discontinued. More recent studies, Rakhshan et al. (2023), question the wisdom of long-term azole maintenance, highlighting concerns such as liver toxicity, drug resistance, and persistent colonization. Thus, symptom suppression without eradication defines a major therapeutic weakness in azole-based management.

Emergence of Non-albicans Candida

A significant concern in RVC management is the rising incidence of non-*albicans Candida* (NAC) species, particularly *C. glabrata* and *C. krusei*. These species are inherently less susceptible—or even resistant—to fluconazole and other azoles (Zakhem et al., 2021). Routine diagnostic workflows often fail to identify the infecting *Candida* species, leading to mismanagement. Akinosoglou et al. (2024) mentioned that azoles remain broadly effective, but this perspective is increasingly challenged by real-world evidence showing that NAC strains dominate in recurrent, treatment-refractory cases, particularly among immunocompetent women with no overt risk factors.

Biofilm-Related Persistence

The role of biofilms in therapeutic failure is now well established. *Candida* biofilms, especially on vaginal mucosa and medical devices, significantly reduce drug penetration and protect fungal cells from host immune responses. Rao et al. (2021) demonstrated that biofilm-embedded *C. albicans* cells could resist azoles up to 1000-fold more than their planktonic counterparts. This barrier renders conventional antifungals ineffective in eradicating infection reservoirs, promoting chronicity.

Lack of Host-Directed Therapy

A major gap lies in the near-exclusive focus on antifungal targeting, with minimal attention to host immune modulation or genetic predispositions. Studies by Mengesha and Conti (2017) emphasised the significance of mucosal immunity, particularly IL-17 pathways, in controlling vaginal Candida colonization. Women with immune deficiencies or polymorphisms in pattern-recognition receptors (e.g., Dectin-1) may experience persistent infection despite appropriate antifungal use. Yet, current treatment protocols are one-size-fits-all, lacking personalization.

Vaginal Microbiota Disruption

Lastly, antifungal therapies often inadvertently disrupt the protective vaginal microbiota, especially *Lactobacillus* spp., which are critical in maintaining an acidic pH and inhibiting *Candida* overgrowth. Akinosoglou et al. (2024) caution that azole-induced dysbiosis predisposes patients to reinfection. However, this crucial factor is often overlooked in clinical practice, and microbiome preservation remains an unaddressed component of standard treatment guidelines.

Although antifungals are available, recurrent vaginal candidiasis (RVC) is poorly treated since there are several treatment gaps that have persisted. The high relapse rates, especially after the discontinuation of the azoles, emphasize the restriction of symptom suppression without actual eradication. Treatment is further complicated by the emergence of azole-resistant non-albicans Candida, biofilm-mediated persistence, and the absence of host-directed therapy. Moreover, routine antifungals tend to alter vaginal microbiota, most notably Lactobacillus spp., making a patient susceptible to reinfection. These challenges show that it is time to go beyond the conventional masses to fit or standard

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treatments of RVC by embracing microbiome-aware and immune-specific intervention strategies concerning personalization.

V. EMERGING THERAPEUTIC APPROACHES

With recurrent vaginal candidiasis (RVC) becoming increasingly resistant to standard azole-based therapies, innovative and multifaceted treatment approaches are essential. New antifungals, immunomodulatory strategies, microbiome-targeted interventions, and precision medicine are redefining the therapeutic landscape.

5.1 Next-generation Antifungals

Ibrexafungerp

Ibrexafungerp, a novel oral triterpenoid that inhibits β-(1,3)-D-glucan synthase, offers potent activity against azole-resistant *Candida* species, including *C. glabrata* and *C. auris*. Phase III data from the VANISH trials (Gamal et al., 2021). demonstrated clinical cure rates of up to 63% in women with VVC, including those with non-*albicans* infections. Unlike echinocandins, which require IV administration, ibrexafungerp's oral route offers substantial convenience. However, some authors, McKiever et al. (2020), caution against overreliance on early-phase trials, pointing out that resistance development and long-term safety data remain unknown, especially in vulnerable groups such as pregnant or immunocompromised women.

Oteseconazole

Oteseconazole, a tetrazole antifungal targeting fungal CYP51, demonstrates superior specificity and fewer off-target effects compared to fluconazole. Martens et al. (2022) showed that oteseconazole achieved >90% sustained clinical remission after a 12-week regimen, even in women with a history of frequent recurrences. Its extended half-life allows for simplified dosing. While proponents argue it represents a major leap in antifungal pharmacology, concerns remain over access and affordability, particularly in low-resource settings.

5.2 Vaginal Microbiome Modulation

Probiotics

Restoring microbial balance via probiotics, particularly strains such as *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14, has been investigated as an adjunctive strategy. Liu et al. (2023) demonstrated that these strains promote vaginal colonization, lactic acid production, and immune modulation. The discrepancy likely stems from variations in dosage, strain specificity, and delivery methods. Some critics argue probiotics offer limited benefit beyond a placebo unless combined with antifungals or administered in high concentrations.

Vaginal Microbiota Transplantation (VMT)

VMT, modelled after fecal microbiota transplantation (FMT), aims to reestablish a stable and protective vaginal microbiome in women with refractory dysbiosis. Meng et al. (2024) demonstrated the potential of VMT in treating resistant bacterial vaginosis. However, its application in RVC is largely theoretical. Ethical issues, lack of standardized donor screening protocols, and potential pathogen transfer limit immediate clinical deployment. Advocates call for rigorous trials, but the intervention remains controversial due to its experimental status.

5.3 Immunotherapy and Vaccines

NDV-3A Vaccine

NDV-3A, targeting the *C. albicans* Als3p adhesin/invasin protein, stimulates Th1 and Th17 immune responses, key in mucosal defense. In a phase II trial, vaccinated women exhibited significantly fewer recurrences over 12 months (Brown et al., 2020). While promising, the vaccine's effectiveness across diverse *Candida* strains and host genotypes is uncertain, and commercial availability remains years away.

Dectin-1 and IL-17 Modulation

Immunomodulation targeting Dectin-1 and IL-17 pathways offers a host-centric approach to enhance mucosal immunity. Gaffen et al. (2018) emphasise that impaired IL-17 signalling contributes to chronic candidiasis. However,

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therapies manipulating these pathways must tread carefully to avoid autoimmune complications. This area remains largely preclinical.

5.4 Biofilm Disruptors

Candida biofilms are notoriously resistant to antifungal agents. Da Silva et al. (2025) mentioned that compounds like EDTA, Farnesol, and DNase have shown potential in disrupting biofilms and enhancing drug penetration. Although in vitro data is encouraging, clinical application is lacking. Topical formulations combining azoles with biofilm disruptors could represent the next generation of adjunctive therapies, but robust human trials are urgently needed.

5.5 Personalized Medicine Approaches

Emerging research highlights the potential of personalized therapy in RVC. Genotyping of *Candida* isolates can guide antifungal selection, especially in azole-resistant infections. Additionally, host genetic screening (e.g., for CARD9 or Dectin-1 mutations) may identify women at heightened risk (Corvilain et al. 2018). Models of prediction, using AI techniques and integrating immunological and microbiome data, are currently under development. Although such tools have great potential for transformations, it is hampered by their high cost, the absence of clinical infrastructures, and data standardization, particularly in low-income environments.

Newer dissolving agents of recurrent vaginal candidiasis (RVC), such as next-generation antifungals, such as ibrexafungerp and oteseconazol, exhibit better pharmacokinetics to treat resistant strains. Probiotics and experimental vaginal microbiota transplantation (VMT) have been tested to modulate the vaginal microbiome to achieve restoration of microbial balance, but human data are still scarce. Host-targeted solutions like the DV-3A vaccine and IL-17/Dectin-1 modulation are described by immunotherapies, having limitations of safety and applicability. Such biofilm disruptors as EDTA and Farnesol appear promising in increasing the efficacy of the antifungal. Genotyping- and AI-based personalized solutions are quite developed yet have an impediment to implementation in cost, infrastructure, and accessibility, particularly in low-resource scenarios.

VI. INTEGRATIVE AND ADJUNCTIVE THERAPIES

Dietary Modifications

All dietary interventions (low-sugar diets, low-yeast diets, and anti-inflammatory diets) have gained appeal in women experiencing recurrent vaginal candidiasis (RVC), following a hypothesis that fungi undergo reduced growth in a sugar-reduced environment. Although anecdotal reports mention the improvement of symptoms, clinical evidence is limited. A very small pilot study by Seelbinder et al. (2023) found carbohydrate-restricted diet was able to reduce Candida colonisation, though the study (n=12) is limited by small sample size. Critics like Hbert and others (2016) say that unless there is a randomized controlled trial, diet should be based on conjecture. In addition, adherence to diet is heterogeneous, and prolonged restriction can have adverse effects on nutritional status. Although some clinicians and patient forums showed enthusiasm about the dietary intervention and its role, the scientific world is still debating the value of dietary intervention minus the microbiome or fungal strain profiling.

Herbal and Natural Agents

The common natural substances, like tea tree oil, garlic, and curcumin, have shown antifungal activity in vitro. Li et al. (2024) demonstrated that the tea tree oil was effective in preventing the C. albicans biofilms, and a natural fungicidal agent, allicin, a product of garlic, was suggested. Nevertheless, such results do not always achieve clinical effectiveness because of bioavailability levels, non-standardizable dose schedules, and the possibility of mucosal irritation. Also, clinical tests are either understudied or not there at all. There are authors like Maglalang et al. (2024) who support the idea of integrative use, although, due to the absence of pharmacokinetic data and safety profiling, it is too early to do so. The existing recommendations support its use with caution, as it may cause allergic reactions or an interaction with other antifungals.

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Hormonal Modulation

The important role of hormonal influences in RVC is ascertained. Candida adhesion and hyphal formation occur to promote Candida adhesion and infection, especially when levels of estrogen are high. According to some studies, including Vercellini et al. (2018), the change from the estrogen-dominant type of birth control to the progesterone-based one could help decrease the recurrence. These recommendations are, nevertheless, grounded on correlative, but not on causative evidence. Strengthening the association of hormone-immunity interaction has to be studied further to make the application of hormonal modulation stamped across the board as an adjunctive therapy.

VII. FUTURE DIRECTIONS AND RESEARCH NEEDS

The dynamic nature of recurrent vaginal candidiasis (RVC) requires a strong, focused research in order to help close the vast gaps in therapy. An urgent requirement is that of head-to-head clinical trials directly comparing the effectiveness and safety of both emerging antifungals (e.g., ibrexafungerp, oteseconazole) and probiotics, and immunotherapies. Existing evidence is disparate, based on small, heterogeneous cohorts, and it cannot be used widely in clinical practice. The other important aspect is the prolonged profile of safety and relapse prevention due to next-generation antifungals. Though newer agents such as ibrexafungerp have some demonstrated promise early in development, their administration to pregnant women, immune-compromised populations, or other variables is untested and currently unknown.

A major problem is the *standardization of the formulations of probiotics* in regard to strain specificity, dose, and route of delivery. The inconsistency that is seen currently in probiotics prevents reproducibility and shatters belief in probiotic adjuncts. Such introduction of microbiome, including vaginal microbiome transplantation (VMT), requires an effective regulatory and ethical framework. Other problems, like the donor screening, the chance of being infected, and informed consent, will have to be dealt with before VMT can be anything but an experimental application.

Lastly, a more *nuanced understanding of host-Candida-microbiota interactions* is needed. Integrative 'omics' approaches—genomics, metabolomics, and microbiomics—may uncover predictive biomarkers for recurrence and guide personalized interventions. Without such insights, treatment will continue to rely on generalised, often suboptimal strategies that fail many women.

VIII. CONCLUSION

In conclusion, recurrent vaginal candidiasis represents a persistent therapeutic challenge, inadequately addressed by existing antifungal strategies, particularly azoles. The gaps — including rising resistance, microbiome disruption, and failure to address underlying host and biofilm factors- necessitate a paradigm shift in management. Emerging therapies like next-generation antifungals, vaccines, probiotics, and personalized medicine approaches offer promising avenues for sustainable, effective treatment. However, robust clinical evidence and long-term data are essential before these can become mainstream. Bridging the gap between symptom control and true long-term remission will require a *multidisciplinary approach* that includes microbiology, immunology, gynecology, and patient-centered care.

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