



Research Article

The ReCiDiF Approach for Recurrent Vulvovaginal Candidosis: Moving from Episodic Treatment to Personalised Maintenance Care

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Abstract

Introduction: Recurrent vulvovaginal candidosis (RVVC) affects up to 7–9% of women of reproductive age and substantially impairs quality of life. Despite its frequency, management remains inconsistent and often empiric, with repeated antifungal exposure, unnecessary lifestyle restrictions, and limited attention to accurate diagnosis or antifungal resistance.

Methods: In this review, we discuss current concepts in the diagnosis and pathophysiology of RVVC, emphasising the importance of microscopic or mycological confirmation, species identification, and targeted susceptibility testing. We review evidence, advantages and disadvantages for antifungal treatment with degressive regimens, such as the ReCiDiF approach, which aims to maintain symptom control while minimising drug exposure and resistance risk.

Conclusions: ReCiDiF offers the best available alternative maintenance treatment regimen currently available. We propose an algorithm to follow up on patients with refractory disease, non-*albicans Candida* infections, and the role of modifiable risk factors, highlighting the limited evidence supporting many commonly imposed behavioural restrictions. Finally, we propose a pragmatic, individualised framework for long-term RVVC management that prioritises diagnostic accuracy, individualized proportional therapy, and preservation of quality of life.

Keywords: Vulvo-vaginitis; Recurrent diseases; Antimycotic resistance; *Candida non-albicans*; *Candida albicans*; Maintenance treatment; Vaccination; Lactobacilli; Probiotic

Introduction

Candida vulvovaginitis (VVC), often referred to as vaginal candidiasis, or more correctly, candidosis, is a common clinical condition caused by overgrowth of *Candida* species, predominantly *Candida albicans*. Approximately 75% of women experience at least one episode during their lifetime, while 7% develop recurrent disease; in women aged 25-34 years this proportion rises to 9% [1]. VVC causes substantial discomfort and negatively affects health-related quality of life. This Personal View focuses on the state-of-the-art diagnostic and therapeutic strategies for recurrent VVC (RVVC).

Definition and diagnosis of RVVC

Definition

RVVC is defined as three or more VVC episodes per year. Management is often challenging because *Candida* may persist in the vaginal mucosa due to a combination of host-related and micro-organism related factors.

Chronic (persistent) or recurrent (relapsing) infections are

more common in women with underlying immune dysfunction, poorly controlled diabetes, HIV infection, pregnancy or use of immunosuppressive therapy. Frequent antibiotic use further disrupts the normal vaginal microbiota, promoting *Candida* overgrowth and relapse.

Clinical presentation of (R)VVC

The most common symptoms are vulvar and/or endovaginal pruritus, sometimes accompanied by burning or pain. Dyspareunia is frequent and penetration may be impossible due to discomfort. Vulvar and vaginal erythema and edema are common, but not obligatory, and interlabial fissures may occur. In complicated cases, the perineal skin can be involved, with erythema, satellite lesions, or perianal involvement. Although curd-like yellowish discharge is considered typical, it is absent in the majority of cases, particularly in RVVC. Odour is usually absent or described as 'sour milk'-like.

Symptom severity can be graded as: (1) mild – intermittent discomfort not present throughout the day or night, (2) moderate – continuous discomfort, with exacerbations that distract from daily activities, but do not prevent them and (3) severe - continuous discomfort that disrupt normal activities, such as nocturnal itching or pain preventing sitting, cycling, or sexual intercourse.

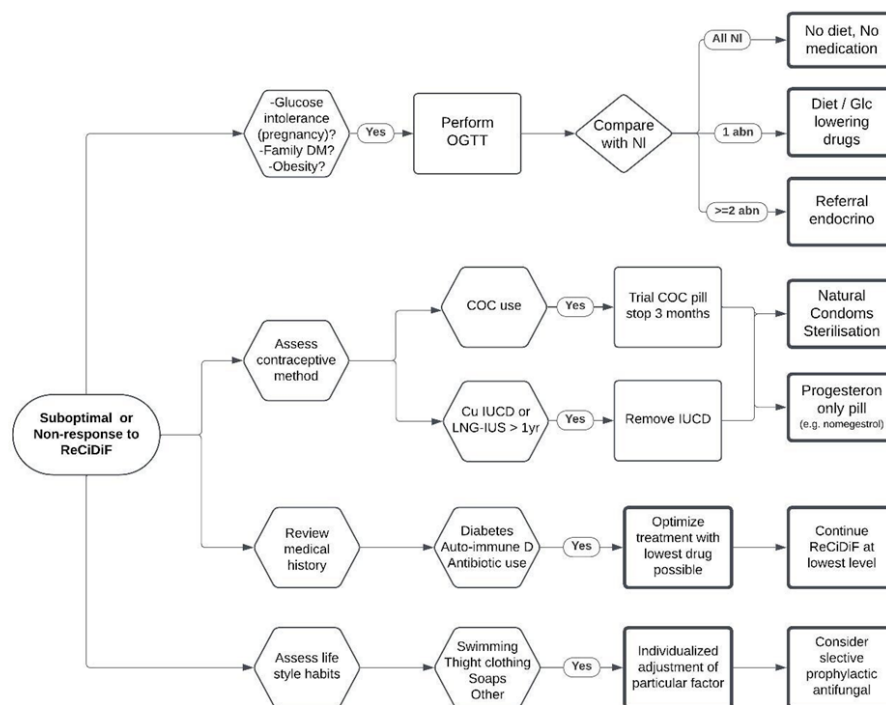


Figure 1: Flow diagram showing ReCiDiF algorithm. RVVC: Recurrent vulvovaginal candidiasis. Fcz/F: fluconazole. Ca: *Candida*.

The clinical picture is straightforward when classical symptoms are present. However, in longstanding or recurrent disease, clinical signs may be subtle, atypical or misleading.

Diagnosis of VVC

Accurate diagnosis is essential for appropriate management. Clinical features overlap with other causes of vaginitis, including aerobic vaginitis (AV), bacterial vaginosis (BV), and trichomoniasis, necessitating careful differential diagnosis. Mixed infections with *Candida* and AV or BV are common.

Diagnostic Methods

Wet-mount microscopy performed immediately after sampling allows visualization of yeast cells (blastospores), pseudohyphae, or hyphae (mycelium) under phase-contrast microscopy [2]. In experienced hands, this rapid, inexpensive technique enables diagnosis of both uncomplicated and complex cases [2]. Vaginal pH measurement is not useful, as *Candida*-associated vaginitis may occur across the full pH spectrum.

Vaginal culture remains the gold standard for species identification, particularly when microscopy is equivocal, and permits antifungal susceptibility testing. Polymerase chain reaction (PCR), including rapid point-of-care assays, offers higher sensitivity and specificity than microscopy and culture, but is limited in routine practice by cost and availability [3].

Differential diagnosis

Lichen sclerosus may occur in younger women and can mimic the lichenoid vulvar changes seen in VVC. *Trichomonas vaginalis* infection may present with discharge and intense pruritus and is often mistakenly treated with repeated antifungal courses. In recurrent *Herpes simplex* infection, pain may be absent, and pruritus may herald an outbreak. Other common causes of vulvar erythema and pruritus include eczema, lichen simplex chronicus, and allergic vulvitis. Lichen planus typically causes sharply demarcated, painful erythematous lesions and is rarely associated with itching.

Pathophysiology

The vaginal ecosystem is normally dominated by *Lactobacillus* species, which help maintain a low pH and inhibit pathogen overgrowth. Antibiotic exposure [4], hormonal fluctuations (eg, pregnancy or contraceptive use) [5], and immune suppression, particularly HIV infection [6], can disrupt this balance, facilitating *Candida* proliferation. Notably, RVVC frequently follows bacteriotherapy that is not always appropriately indicated.

Innate immune responses mediated by neutrophils and macrophages play a central role in controlling *Candida*. Cell-mediated immunity is not the primary host defence in RVVC, and its dysfunction does

not trigger disease [7]. Recent studies demonstrate an imbalance in Th1/Th2 responses in RVVC, with increased interferon- γ , tumour necrosis factor, interleukin (IL)-17 [8], IL-1, and IL-8 [9], and reduced IL-10, IL-4, and IL-6 compared with episodic VVC [10].

Therapeutic strategies of RVVC

Anti-fungal medication

Topical azole antifungals, including miconazole, clotrimazole, terconazole, econazole, fenticonazole, and butoconazole, disrupt fungal cell membranes and are typically administered for 3–7 days as creams, suppositories, or tablets [11]. Cure rates exceed 80%, with fewer systemic adverse effects than oral agents [1].

Oral antifungals, primarily fluconazole (150 mg single dose) or itraconazole (200 mg daily for 2 days), are recommended first-line therapies for uncomplicated acute VVC [11,12], achieving cure rates of 80–90% in clinical trials [13].

In pregnancy, oral azoles are contraindicated because of reported associations with congenital abnormalities at high doses [14] and increased risk of miscarriage and preterm delivery [15]. Although these risks were not confirmed in other large, well-designed studies [16,17], topical azoles are preferred and considered safe during pregnancy.

Adjunctive Therapies

Probiotics

Probiotics containing *Lactobacillus* species have been proposed for treatment and recurrence prevention, clinical evidence remains weak [18–20]. *Saccharomyces* species are also under investigation, alone, or combined with lactobacilli [21,22].

Empiric and intermittent treatment

In most women, no clear underlying risk factor is identified. If recurrences are infrequent or mild, intermittent self-treatment with short courses of vaginal or oral antifungals may be attempted, occasionally combined with mild topical corticosteroids for severe pruritus. This approach carries risks, including escalating doses, prolonged treatments, frequent drug switching, or adoption of unproven interventions such as restrictive “*Candida* diets” or immune-enhancing therapies.

Treatment of sexual partners is frequently advised but is not recommended, except in rare cases of penile candidosis unrelated to intercourse.

Maintenance Strategies

Women with frequent recurrences benefit from suppressive maintenance therapy. Weekly oral or vaginal azole regimens were first proposed decades ago. The most widely used protocol—

fluconazole 150 mg weekly for 6 months—significantly reduces recurrences in up to 80% of patients during treatment [23]. However, many women relapse after abrupt discontinuation, and some may be overtreated. Prolongation of fixed high-dose regimens is discouraged because of resistance concerns.

To address these limitations, the ReCiDiF regimen (Recurrent Candida Infection prevention using Degressive doses of Fluconazole) was developed [24] and is now recommended in several international guidelines [11,12,25].

ReCiDiF principles

ReCiDiF aims to maintain symptom control while using the lowest effective antifungal dose, thereby minimising resistance risk. Women with ≥ 3 VVC episodes per year are eligible (**Figure 1**). Because microscopy is often underused in clinical practice, vaginal culture is required to confirm *Candida* infection [26]. When cultures are negative at consultation, home self-sampling increases diagnostic sensitivity from 17% to 82% [27]. In discordant cases, nucleic acid amplification tests (NAATs) may be helpful [3].

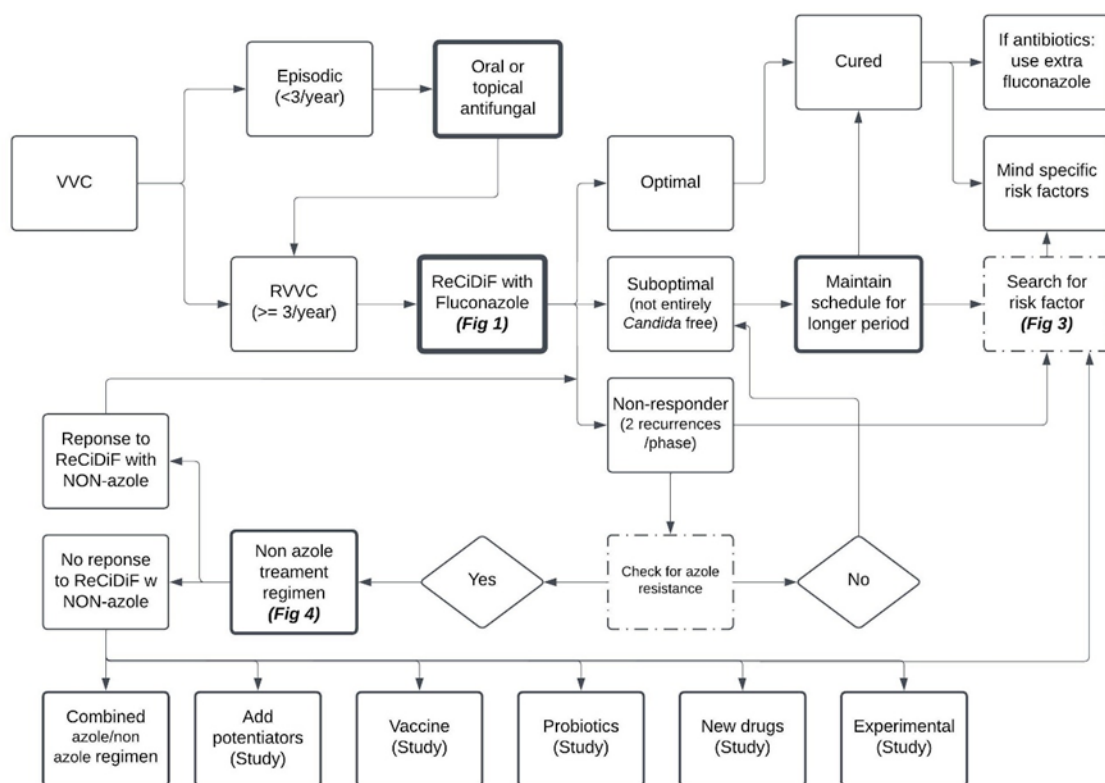


Figure 2: Treatment regimen in function of response to ReCiDiF. VVC: Vulvovaginal Candidosis. RVVC Recurrent VVC.

Approximately 25–30% fail to progress (*non-responders*). In these cases, repeat species identification, resistance testing, and systematic risk-factor assessment (Figure 3) are recommended [28], followed by alternative azole or non-azole therapies (Figure 4). Their treatment trajectory is complicated and often requires specialized advice.

infections, nor does it reliably predict future susceptibility [43]. Minor variations in susceptibility testing methods significantly impacted MIC results and their correlation with *in vivo* responses

[44], depending on various factors, including medium composition and pH [45]. This contrasts with bacterial antibiotic resistance testing, where such correlations are typically more reliable.

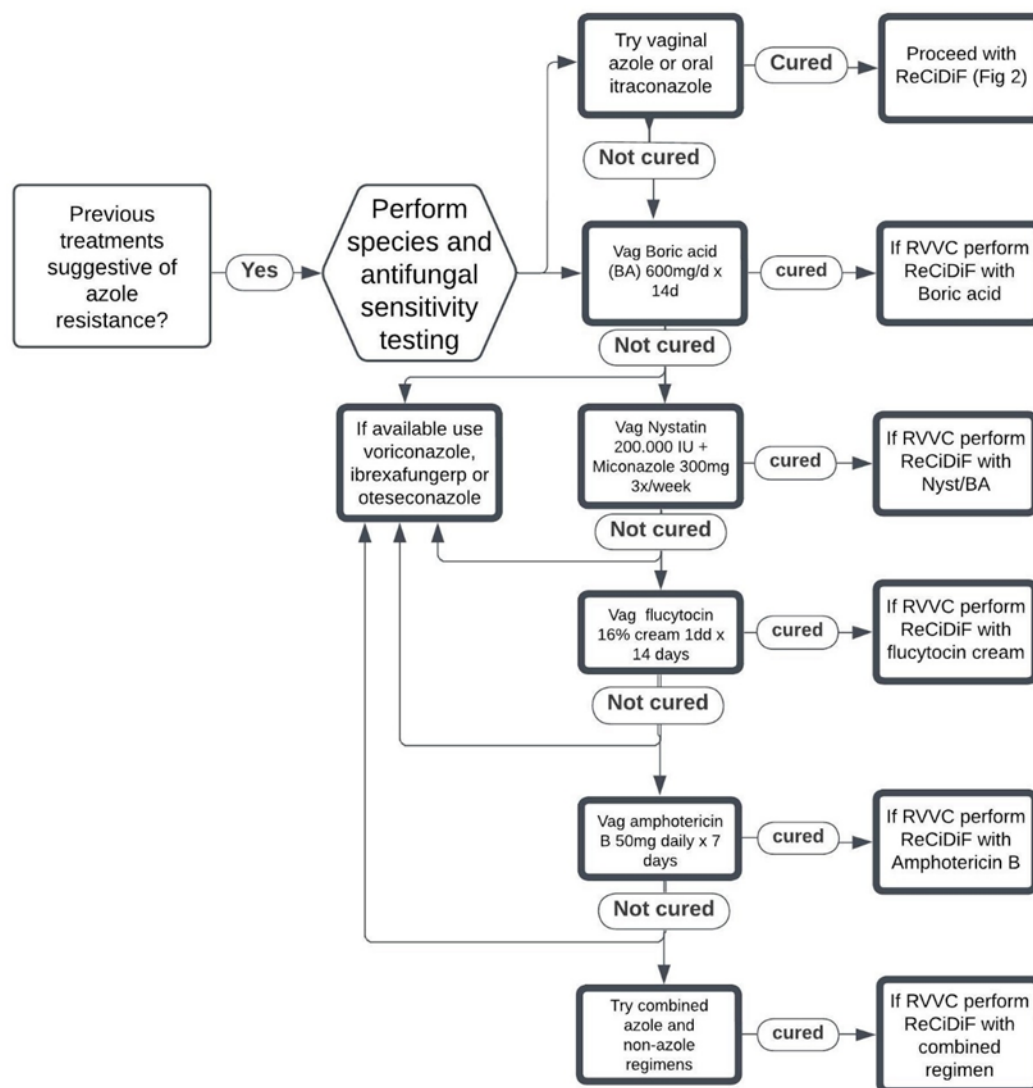


Figure 4: Mode of action in cases of antifungal resistance. RVVC: Recurrent vulvovaginal candidiasis. Nyst: nystatine. BA: boric acid. Vag: vaginal application.

Therapy in case of fluconazole resistance

If a patient seems refractory to fluconazole treatment, and/or resistance is discovered, higher doses of fluconazole (e.g. 400mg per week or every 2 weeks) or a switch to other azoles (e.g. oral itraconazole, of vaginal miconazole, fenticonazole, butoconazole, or clotrimazole) may be attempted, but not for a long period, as high doses may have a higher risk to side effects, such as liver damage (Figure 4). If responsive, a similar regimen as ReCiDiF will therefore be followed, in order to decrease the total dose to the minimum possible. If non-responsive, or a non-*albicans* species is documented, 600mg vaginal boric acid ovules can be given, daily at bedtime for 14 days, followed by a degressive regimen with boric acid (Figure 4, top). If this fails, a next second line treatment with vaginal ovules composed of 250.000IE nystatin (with or without miconazole) can be installed, subsequently following along the same degressive treatment principles. Next steps in refractory cases can be a ReCiDiF regimen using vaginal 16% flucytosin in a cream, vaginal tablets of 50mg amphotericin B or a combined azole/non azole treatment (Figure 4).

The newer azole drugs, like etoseconazole, and non-azole, like ibrexafungerp, are very efficacious for recurrence prevention in RVVC patients, but like most of the other second line products mentioned above, are often difficult to obtain in many countries and require intensive international collaboration between colleagues and pharmacies.

For rare cases unresponsive to above treatments, we rely on *experimental new therapies*, such as azole potentiators, probiotics, new azole or non-azole drugs and vaccines, mostly in the context of clinical trials. An overview of these new and experimental drugs and future management tools was recently published by our group [28].

Risk factors and consequent management

Physicians often respond to RVVC by imposing numerous restrictions—dietary bans, contraceptive changes, hygiene rules, clothing modifications, or sexual limitations—despite limited evidence for most measures. These restrictions frequently impair quality of life without improving outcomes. We therefore recommend avoiding cumulative “don’t do’s” unless justified. A careful history linking symptom episodes with menstrual timing, antibiotic use, or intercourse often provides more meaningful guidance and can support targeted 2–3-month trials of modifying single suspected risk factors.

Glucose metabolism. Severe and frequent VVC episodes are well known in women with poorly controlled diabetes. Night-time hyperglycemia may be missed on daytime logs; elevated nocturnal values or high HbA1c levels may uncover dysregulated glycemia leading to increased susceptibility for vaginal *Candida* recurrences

[46]. This prompted our comparative study of glucose metabolism in RVVC patients versus age-matched controls without VVC [47]. RVVC patients showed a 15% higher mean area-under-the-curve during standardized 75 g OGTT ($p=0.01$) and a 25% higher mean HbA1c ($p=0.006$), independent of age and BMI. Although none had diabetes or prediabetes, three times more patients exceeded the 95th percentile for glucose levels ($p=0.016$) [47].

However, among ReCiDiF non-responders we found no differences in urinary glucose, OGTT glycemia, or diabetes history (including gestational) compared with responders [48]. Therefore, rather than imposing restrictive diets or unproven “yeast-reducing” regimens, we recommend performing an OGTT and comparing values with controls before initiating glucose-lowering interventions. For isolated post-OGTT elevations, we advise reducing fast carbohydrates and consider 500–800 mg metformin plus weight management as needed. When ≥ 2 OGTT values are elevated or fasting glycemia exceeds 126 mg/dl, endocrinology referral is indicated. In our surveillance, these targeted interventions significantly improved RVVC in several patients [49].

Hormonal fluctuations influence symptomatic VVC. Many patients experience relief during menses but flare pre- or post-menstrually. For women with regular cycles, we schedule the monthly ReCiDiF dose around day 21, corresponding to peak hormonal levels.

Historically, high-estrogen contraceptive pills (≥ 50 μ g ethinyl estradiol) increased VVC recurrence. Although lower-dose COCs are assumed safer, no studies have evaluated this in sensitive patients. Given that estrogen likely exerts a dose-dependent rather than threshold effect, a 2–3-month trial discontinuing COCs is reasonable in women reporting cycle-related symptoms, or a temporary switch to a progestin-only pill (POP) or injectable progesterone. Evidence suggests such switches may decrease *Candida* growth [50,51], and in our own lifestyle-adjustment surveys many women reported improvement after changing from estrogen-containing pills to POP regimens [49,52]. In postmenopausal women, symptomatic VVC is rare, unless on hormone replacement therapy.

We also evaluated whether the **levonorgestrel-releasing intrauterine system (LNG-IUS)** could help RVVC-susceptible women due to its progestin dominance and tendency to induce amenorrhea, which may also benefit women with recurrent BV. Surprisingly, retrospective [53], cross-sectional [52], and prospective [54] studies showed no meaningful impact on vaginal microbiota. *Candida* morphotypes (hyphae, pseudohyphae, blastospores) were, however, more prevalent—especially after one year of use. Thus, if RVVC worsens one or more years after LNG-IUS insertion and other factors have been excluded, device removal may be beneficial.

Immune alterations have long been suspected in RVVC [55]. One study suggested increased vaginal Th1 response contributes to symptomatic infection [56]. In ReCiDiF, non-responders exhibited significantly more atopic disease in personal and family history, supporting an immune-overreaction phenotype in some patients [57]. These patients may benefit from intermittent addition of mild topical corticosteroids (e.g., 0.025% betamethasone) alongside ReCiDiF.

Genetic analyses show innate immune defects—particularly mannose-binding lectin polymorphisms—are more common in RVVC patients than controls [58,59].

Antibiotics use is a well-recognized trigger of VVC. RVVC onset is often linked to preceding antibiotic exposure, especially when prolonged or repeated. A recent pilot study showed even short-course antibiotics tripled asymptomatic *Candida* colonization and significantly increased symptomatic VVC versus controls [60]. Colonization rates rise from 21% to 37% post-antibiotics, with *C. albicans* predominating[†]. Tetracyclines, penicillins, and macrolides are associated with higher risk [61], though all antibiotics can contribute [4]. Patients may be unaware of perioperative antibiotic exposure, which could explain unexpected recurrences. Symptoms typically manifest 2–3 weeks after treatment [62].

Patients should avoid antibiotics unless clearly indicated. Nevertheless, inappropriate prescribing remains common, and many patients obtain antibiotics independently without medical guidance. When antibiotics are necessary, co-administration of probiotics may reduce VVC breakthroughs [63]. However, most probiotics are designed for BV or AV prevention and are insufficiently evaluated for VVC [63,64]. Laboratory-selected lactobacilli show promise in treating or preventing VVC, though results remain variable [18,20,65].

Lifestyle & hygienic factors are frequently suspected contributors. In our survey, many women reported symptom improvement after adopting gentler perineal care [49], including switching from regular soap to pH-neutral products or avoiding soaps entirely; minimizing bathing in favor of showering; changing wet bathing clothes promptly; avoiding tight underwear or jeans; and minimizing exposure to sanitary pads.

Evidence supporting these measures, however, is mixed. In Bardin et al.'s study women with VVC used more often bactericidal soap than healthy women (64.6% vs. 37.8%, $p<0.001$), suggesting microbiota disruption [66]. In contrast, intimate soaps and wet wipes were more frequent in healthy controls than in women with *Candida* or BV (36% vs. 12.7%, $p<0.001$). Sexual behaviours such as anal intercourse and use of sex toys were more common among women with VVC (22.8% and 17.7%) versus controls (10.1% and 5.8%, $p=0.018$ and $p=0.006$) [66]. However, frequency of intercourse, number of partners, hair removal, and menstrual

hygiene showed no association [66].

Multiple-site *Candida* colonization, especially oral and anal, correlated with non-response in RVVC [67], yet sexual practices themselves were not linked to colonization or treatment failure [68].

Clothing and sanitary products may influence local moisture and temperature. A Nigerian study found higher VVC prevalence in women wearing nylon/synthetic underwear (76.8%) compared with cotton (42.9%) [69]. In Xi'an, risk factors included inadequate vulvar hygiene before or after intercourse and frequent intravaginal douching [70]. A Brazilian study associated synthetic underwear with vulvovaginitis, but found no link with sanitary pad use [71].

Conversely, a clinical trial showed that briefs, with antimicrobial fibroin fabric, without concurrent antifungals, produced greater symptom reduction and fewer recurrences in RVVC patients than cotton underwear [72]. Continual panty-liner use increased recurrence risk (OR 3.97) [73], and reusable pads increased urogenital infection risk versus disposable pads (AdjOR 2.8) [74].

Practical approach

Lifestyle changes may help selected patients, but broad or cumulative restrictions are unnecessary and often harmful. We recommend trialing *one* potential factor for 2–3 months and discontinuing it if ineffective. Even with thorough assessment, no identifiable risk factor emerges in roughly 50% of patients. Lack of identifiable risk should *not* justify continued imposition of unproven bans, as these fuel patient guilt.

Partner treatment also has no role. Antimycotic treatment of sexual partners neither prevents recurrences nor reduces colonization, and carries risks of toxicity, allergy, and resistance. Importantly, it reinforces the false notion of sexual transmission, potentially causing psychological strain and unwarranted suspicion within relationships.

Management of Special Populations

Pregnancy

Pregnant women with VVC should avoid oral antifungals due to the risk of teratogenicity. While oral antifungals are not recommended due to potential fetal risks [75], topical therapies like 2% miconazole and clotrimazole are preferred during pregnancy due to their safety and efficacy [1,75]. Prophylactic treatment in the last trimester for asymptomatic VVC may improve outcomes according to some, but remains debated [75]. Despite some studies claiming VVC is a cause of preterm birth, most large and well-controlled studies contradict this. We currently do not advise treatment of asymptomatic *Candida* vulvovaginitis in pregnant women.

When patients on a ReCiDiF regimen are or intend to become pregnant, any oral ReCiDiF treatment should be arrested. Only if relapses occur during pregnancy, a ReCiDiF regimen using vaginal antifungals can be installed. Remarkably, although pregnancy is considered to be a risk factor for developing RVVC, in our experience patients with previous RVVC often experience less or no recurrences during pregnancy.

Immunocompromised Patients

Women with HIV, diabetes, or those undergoing chemotherapy are more likely to experience frequent and severe *Candida* infections. These patients require more aggressive and prolonged treatment strategies, including systemic antifungal therapy and close monitoring for complications.

Post-Menopausal Women

Post-menopausal women may experience *Candida* infections due to changes in vaginal pH and oestrogen levels. Local oestrogen therapy in combination with antifungal treatment may be necessary for effective management, although advocating such approach is risky as oestrogenisation of the vagina in menopausal women can also increase the recurrence and severity rate of RVVC.

Side Effects and Safety Considerations

While antifungal treatments are generally well-tolerated, they can cause side effects. Topical antifungals may cause local irritation, while oral antifungals like fluconazole theoretically can lead to gastrointestinal symptoms or liver toxicity. However, in the doses we use in the ReCiDiF regimen, liver function derangements have never been encountered. Skin lesions due to allergy against fluconazole, can seldomly occur and necessitate arresting using the drug. Finally, as discussed above, long-term use of antifungals, particularly fluconazole, increase the risk of developing azole resistance.

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