Treating recurrent vulvovaginal candidiasis

Vulvovaginal candidiasis can be a clinical challenge in patients with recurrent episodes. Here, a discussion of treatment options for infections caused by *Candida albicans* and non-*albicans* species and azole-resistant isolates, plus a recently approved drug for recurrent infection for induction and maintenance therapy

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IN THIS ARTICLE

Recurrent vulvovaginal candidiasis (RVVC) is a common cause of vaginitis and gynecologic morbidity in the United States and globally.[1] RVVC is defined as at least 3 laboratory-confirmed (for example, culture, nucleic acid amplification test [NAAT]) symptomatic episodes in the previous 12 months.[2] Common symptoms include vulvar pruritus, erythema, local skin and mucosal irritation, and abnormal discharge that may be thick and white or thin and watery.

The true incidence of RVVC is difficult to determine due to clinical diagnostic inaccuracy that results in over- and underdiagnosis of VVC and the general availability of over-the-counter topical antifungal medications that individuals who self-diagnose use to treat VVC.[3]

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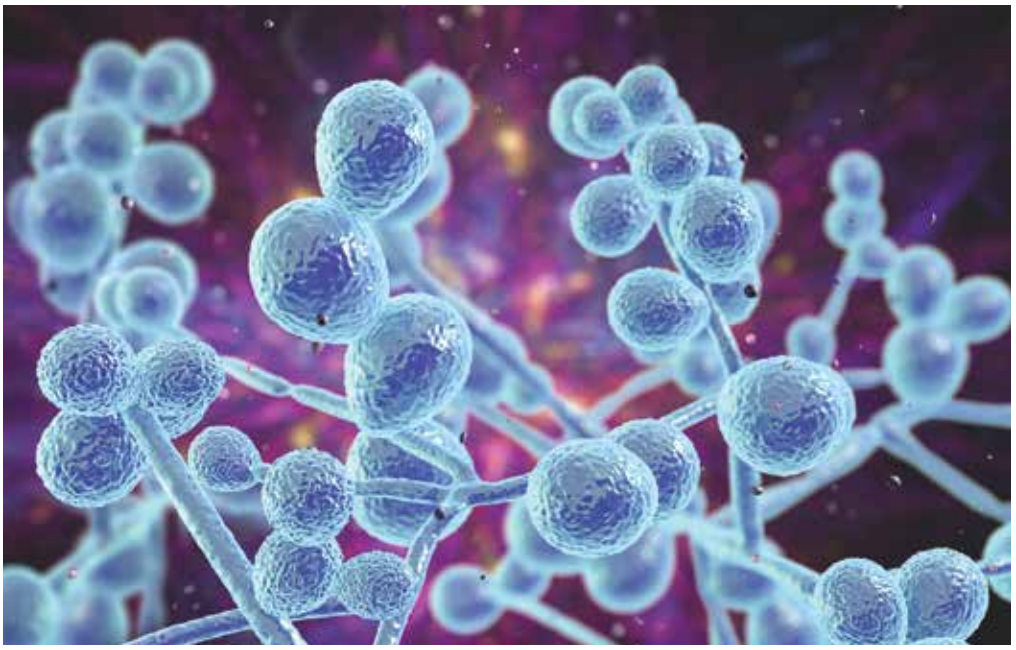
Causative organisms

Vulvovaginal yeast infections are caused by *Candida* species, a family of ubiquitous fungi that are a part of normal genitourinary and gastrointestinal flora.[4] As such, these infections are commonly termed VVC. The presence of *Candida* species in the vagina without evidence of inflammation is not considered an infection but rather is more consistent with vaginal colonization. Inflammation in the setting of *Candida* species is what characterizes a true VVC infection.[4]

Candida albicans is responsible for the vast majority of VVC cases in the United States, with *Candida glabrata* accounting for most of the remaining infections.[5] The majority of RVVC infections that are caused by *C albicans* are due to azole-sensitive strains (85%–95% of infections).[2] *C glabrata*, by contrast, is intrinsically resistant to azoles, which is thought primarily to be due to overexpression of drug efflux pumps that remove active drug from the cell.[6,7]

Why does VVC reoccur?

The pathogenesis of RVVC is not well understood. Predisposing factors may



include frequent or recent antibiotic use, poorly controlled diabetes, immunodeficiency, and other host factors. However, many cases of RVVC are idiopathic and no predisposing or underlying conditions are identified.[7]

The role of genetic factors in predisposing to or triggering RVVC is unclear and is an area of ongoing investigation.[2] Longitudinal DNA-typing studies suggest that recurrent disease is usually due to relapse from a persistent vaginal reservoir of organisms (that is, vaginal colonization) or endogenous reinfection with identical strains of susceptible *C albicans*.[8,9] Symptomatic VVC likely results when the symbiotic balance between yeast and the normal vaginal microbiota is disrupted (by either *Candida* species overgrowth or changes in host immune factors).[2] Less commonly, "recurrent" infections may in fact be due to azole-resistant *Candida* and non-*Candida* species.[2]

Clinical aspects and diagnosis of VVC

Signs and symptoms suggestive of VVC include vulvovaginal erythema, edema, vaginal discharge, vulvovaginal pruritus, and irritation. Given the lack of specificity of individual clinical findings in diagnosing VVC, or for distinguishing between other common causes of vaginitis (such as bacterial vaginosis and trichomoniasis), laboratory testing (that is, microscopy) should be performed in combination with a clinical exam in order to make a confident diagnosis of VVC.[10] Self-diagnosis of VVC is inaccurate and is not recommended, as misdiagnosis and inappropriate treatment is cost ineffective, delays accurate diagnoses, and may contribute to growing azole resistance.

In patients with signs and symptoms of VVC, saline and potassium hydroxide microscopy should be performed.[7] **TABLE 1** summarizes other major diagnostic techniques for VVC.

Diagnostic considerations

Non-*albicans Candida* species, such as *C glabrata*, may be associated with minimally symptomatic or completely asymptomatic infections and may not be identified easily on wet mount as it does not form pseudohyphae or hyphae.[11] Therefore, culture and susceptibility or NAAT testing is highly recommended for patients who remain symptomatic and/or have a nondiagnostic microscopy and a normal vaginal pH.[7]

FAST TRACK

Laboratory testing (that is, microscopy) should be performed in combination with a clinical exam in order to make a confident diagnosis of VVC

CONTINUED ON PAGE 24

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CONTINUED FROM PAGE 23

TABLE 1 Diagnostic techniques for vulvovaginal candidiasis

Test	Timing of results	"Positive" result interpretation	Comments
Saline and 10% potassium hydroxide (KOH) microscopy plus vaginal pH	Immediate	pH: < 4.5 Wet prep: budding yeasts, hyphae, or pseudohyphae	Low sensitivity of microscopy for VVC (40%–70%)
Commercial NAAT	> 24 hours	1 or more *Candida* species identification	Costly, high sensitivity and increased accuracy VVC diagnosis,[24-26] acceptable for patient self-collection
DNA direct probe assay	Several hours	Color indicator turns blue when *Candida* species detected	Costly, does not provide *Candida* organism speciation
Culture with or without speciation	1–2 days for *albicans* species. *Candida glabrata* may take several days to grow	Growth of yeast species	Vaginal colonization with *Candida* species is common (up to 20%).[7] Positive cultures in the absence of VVC signs/symptoms is not a treatment indication

Abbreviations: NAAT, nucleic acid amplification test; VVC, vulvovaginal candidiasis.

FAST TRACK

During pregnancy, only topical azole therapy is recommended for use, given the potential risk for adverse fetal outcomes (spontaneous abortion, congenital malformations) with fetal exposure to oral fluconazole ingested by the pregnant person

Treatment options

Prior to May 2022, there had been no drugs approved by the US Food and Drug Administration (FDA) to treat RVVC. The mainstay of treatment is long-term maintenance therapy to achieve mycologic remission (**TABLE 2**).

In general, recurrent episodes of VVC should be treated with a longer duration of therapy (for example, oral fluconazole 150 mg every 72 hours for a total of 3 doses or topical azole for 7–14 days).[7] If recurrent maintenance/suppressive therapy is started, the induction phase should be longer as well, at least 10 to 14 days with a topical or oral azole followed by a 6-month or longer course of weekly oral or topical azole therapy (such as 6–12 months).[12,13]

Patients with underlying immunodeficiency (such as poorly controlled diabetes, chronic corticosteroid treatment) may need prolonged courses of therapy. Correction of modifiable conditions and optimization of comorbidities should be prioritized—for example, optimized glucose control, weight loss, durable viral suppression, and so on. Of note, symptomatic VVC is more frequent among individuals with HIV and correlates with severity of immunodeficiency. Pharmacologic options for RVVC for individuals with HIV do not differ from standard recommendations.[14]

Fluconazole

Fluconazole is a safe, affordable, and convenient prescription oral medication that can be used for initial and maintenance/suppressive therapy.[2] Fluconazole levels in vaginal secretions remain at therapeutic concentrations for at least 72 hours after a 150-mg dose.[15] Induction therapy consists of oral fluconazole 150 mg every 72 hours for a total of 3 doses, followed by a maintenance regimen of a once-weekly dose of oral fluconazole 150 mg for a total of 6 months. Unfortunately, up to 55% of patients will experience a relapse in symptoms.[12]

Routine liver function test monitoring is not indicated for fluconazole maintenance therapy, but it should be performed if patients are treated with daily or long-term alternative oral azole medications, such as ketoconazole and itraconazole.

During pregnancy, only topical azole therapy is recommended for use, given the potential risk for adverse fetal outcomes, such as spontaneous abortion and congenital malformations, with fetal exposure to oral fluconazole ingested by the pregnant person.[16] Fluconazole is present in breast milk, but it is safe to use during lactation when used at recommended doses.[17]

CONTINUED ON PAGE 28

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to estrogens and progestins before conception or during early pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids or endometriosis reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no observed adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold lower than that in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD).

8.2. Lactation

Risk Summary

There are no data on the presence of relugolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix was detected in milk in lactating rats *[see Data]*. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.

Data

Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3. Females and Males of Reproductive Potential

Based on animal data and the mechanism of action, MYFEMBREE can cause early pregnancy loss if MYFEMBREE is administered to pregnant women.

Pregnancy Testing

MYFEMBREE may delay the ability to recognize pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding. Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE and discontinue treatment if pregnancy is confirmed.

Contraception

Advise women of reproductive potential to use effective non-hormonal contraception during treatment with MYFEMBREE and for 1 week following discontinuation. Avoid concomitant use of hormonal contraceptives with MYFEMBREE. The use of estrogen-containing hormonal contraceptives may increase the risk of estrogen-associated adverse events and is expected to decrease the efficacy of MYFEMBREE.

8.4. Pediatric Use

Safety and effectiveness of MYFEMBREE in pediatric patients have not been established.

8.6. Hepatic Impairment

MYFEMBREE is contraindicated in women with hepatic impairment or disease. The use of E2 (a component of MYFEMBREE) in patients with hepatic impairment is expected to increase the exposure to E2 and increase the risk of E2-associated adverse reactions.

10. OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding.

Supportive care is recommended if an overdose occurs. The amount of relugolix, estradiol, or norethindrone removed by hemodialysis is unknown.

Please see full Prescribing Information for Patient Counseling Information.

This Brief Summary is based on MYFEMBREE Prescribing Information dated August 2022, which can be found at MYFEMBREE.com.

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Treating recurrent vulvovaginal candidiasis

CONTINUED FROM PAGE 24

Options for fluconazole-resistant *C albicans* infection

Patients who have RVVC with frequent and/or prolonged use of fluconazole are at risk for developing azole-resistant isolates of *C albicans*.[12] For patients found to have azole-resistant infections, treatment options include increasing the azole dose based on isolate minimal inhibitory concentrations (MIC) to various antifungals, therapy with a non-fluconazole azole regimen, or switching to a different therapeutic drug class altogether.[7]

Options for non-*albicans* *Candida* species infection

Given the intrinsic resistance to azole therapy in some non-*albicans Candida* species (specifically *C glabrata and Candida krusei*), boric acid or nystatin regimens can be used. An induction course of vaginal boric acid is given as 600 mg per vagina daily for up to 14 days and is associated with a 70% rate of mycologic control.[7] Boric acid is known to cause local irritation and dermatitis for both the patient and any sexual partners. If ingested orally, boric acid is associated with significant toxicity and even death.[7]

Vaginal nystatin also may be considered, with an induction course of 100,000 U for 14 days, with a similar regimen recommended for maintenance therapy. However, data are limited on maintenance regimens for RVVC due to non-*albicans Candida* species.[2]

Gentian violet

Gentian violet is a topical antiseptic agent that is available over the counter. Use of this agent

TABLE 2 Treatment of recurrent vulvovaginal candidiasis[2,7,13]

Azole	Route	Induction	Maintenance
Fluconazole regimens	Oral, single-drug regimen	Fluconazole 150 mg every 72 hours (3 doses total)	Fluconazole 150 mg once per week for 6 months
	Combination oral and topical	Oral and/or topical regimen: 10–14 days of topical azole or oral azole	• Fluconazole 150 mg once per week for 6 months OR • Topical azole therapy for 6 months (clotrimazole 200-mg vaginal cream twice weekly or 500-mg vaginal suppository once weekly)
Oteseconazole regimens	Oral, single-drug regimen	Week 1: Day 1: 600 mg, as a single dose Day 2: 450 mg, as a single dose	Weeks 2 to 12: 150 mg, as a single dose, on day 14, then 150-mg once weekly for 10 weeks
	Oral, dual-drug regimen	Days 1 to 7: **fluconazole** 150 mg, as a single dose, on days 1, 4, and 7 Days 14 to 20: **oteseconazole** 150 mg once daily	Starting on day 28: **oteseconazole** 150 mg once weekly for 11 weeks
Itraconazole regimens	Oral	200 mg twice a day for 3 days	100–200 mg/day for 6 months
Topical regimens	Topical, single-drug regimen	Miconazole 2% vaginal cream for 7 nights Miconazole 4% vaginal cream for 3 nights	Miconazole 1,200-mg vaginal suppository once weekly for 6 months
	Topical, dual-drug regimen	Clotrimazole 1% vaginal cream for 7 nights Clotrimazole 2% vaginal cream for 3 nights Tioconazole 6.5% ointment for 1 night Terconazole 0.4% vaginal cream for 7 nights Terconazole 0.8% vaginal cream for 3 nights Terconazole 80-mg vaginal suppository for 3 nights Butoconazole 2% vaginal cream single dose	Miconazole 1,200-mg vaginal suppository once weekly for 6 months
Non-azole and/or *Candida glabrata* regimens	Vaginal, single-drug regimen	Boric acid: vaginal suppository/capsule 600 mg daily for 14 days	No data to support a maintenance regimen dosing
	Vaginal, single-drug regimen	Nystatin: 100,000-U suppository per vagina daily for 14 days	
Azole-resistant regimens	Vaginal, single-drug regimen	Amphotericin B: vaginal cream/suppositories 5%–10% nightly for 14 days	None
	Vaginal, single-drug regimen	Flucytosine cream: 17% per vagina daily, nightly for 14 days	None
		Boric acid (see regimen above)	
		Nystatin (see regimen above)	

CONTINUED ON PAGE 30

CONTINUED FROM PAGE 29

is uncommon given the availability of highly effective azole-based therapy. Although useful due to its antipruritic properties, gentian violet can be messy to use and tends to stain clothing permanently.

Gentian violet use may be considered in cases of refractory RVVC with or without azole-resistant infections; it is applied as a 1% or 2% solution directly to affected areas for 10 to 14 days.[18]

Lactobacilli probiotics and dietary changes

Data that support the oral and/or vaginal use of probiotics that contain live lactobacilli are conflicting. In the absence of conclusive evidence to support probiotic use to treat and prevent RVVC, as well as variable quality of available products, use of these agents is not recommended.[19]

No controlled studies have evaluated the role of various diets in preventing RVVC; thus, no specific dietary changes are recommended.

Behavioral therapy

Available evidence does not support the treatment of sexual partners of patients with RVVC.[7]

FAST TRACK

For patients whose symptoms do not respond to oral fluconazole therapy, oteseconazole is now available as a noninferior treatment option to fluconazole for both induction and maintenance therapy

What's new in treatment?

Until recently, the main standard of care for RVVC has been oral fluconazole-based therapy. For patients whose symptoms do not respond to oral fluconazole therapy, oteseconazole is now available as a noninferior treatment option to fluconazole for both induction and maintenance therapy. Like other azoles, oteseconazole works by inhibiting a fungal enzyme (CYP51) that is essential in fungal cell membrane integrity and fungal growth.[20] Oteseconazole is a more selective inhibitor of the fungal CYP51 enzyme and has demonstrated excellent potency against *Candida* species in in vitro pharmacologic studies.[21]

In a phase 3 study that evaluated the safety and efficacy of oteseconazole in the treatment and prevention of RVVC, oteseconazole was found to be both safe and efficacious in both the induction and maintenance phases of treatment for RVVC.[20] In this trial, induction and maintenance with oteseconazole was compared with induction with fluconazole and placebo maintenance. Among the 185 participants with culture-verified RVVC, the oteseconazole regimen (n = 123) was associated with fewer recurrences of culture-verified VVC infections than was the fluconazole induction/placebo maintenance regimen (n = 62) during the 48-week maintenance phase of therapy (5% vs 42%).[20]

Single- and dual-drug dosing regimens of oteseconazole are recommended based on previous trial data that compared safety and efficacy of oteseconazole versus fluconazole induction therapy and oteseconazole versus placebo maintenance therapy.[22] However, widespread use of oteseconazole regimens are limited due to its higher costs and limited access to the drug outside of a research setting.[20]

Single-drug induction therapy with oteseconazole consists of a single 600-mg oral dose on day 1 followed by a second dose of 450 mg orally on day 2. Starting on day 14, maintenance therapy starts with a single oral dose of 150 mg and is continued weekly for 11 weeks.[22]

Dual-drug induction therapy consists of oral fluconazole 150 mg on days 1, 4, and 7 followed by daily dosing of oral oteseconazole 150 mg on days 14 through 20. Then, starting on day 28, weekly dosing of oral oteseconazole 150 mg is continued for 11 weeks.[22]

Effects on pregnancy and lactation. Concerns of oteseconazole's fetal teratogenicity are based on animal reproduction studies that reported ocular abnormalities from in utero exposure. Human data are insufficient to determine if oteseconazole is excreted in breast milk or what its effects are on milk production. Among breastfed infants whose mothers were exposed to oteseconazole during lactation, no adverse outcomes were reported, but follow up of oteseconazole-exposed infants was limited.[22] Therefore, use of oteseconazole among pregnant and/or lactating persons with RVVC is contraindicated at this time. The long-half life (approximately 138 days) of oteseconazole may preclude use among persons attempting pregnancy.[22]

CONTINUED ON PAGE 32

CONTINUED FROM PAGE 30

Other therapies. The other common classes of antifungal therapy used in the treatment of RVVC include the polyenes (for example, amphotericin B) and echinocandins (such as caspofungin) drug classes. Emerging azole-resistance among *Candida* species has been recognized as a significant concern from the Centers for Disease Control and Prevention.[7] Echinocandins, which are generally better tolerated and have a lower adverse side effect profile than polyenes, are a promising therapeutic class, but currently they are limited to intravenous options. SCY-078, a novel oral echinocandin in development, has shown in vitro fungicidal activity against multiple *albicans* and non-*albicans Candida* species in pharmacokinetic/pharmacodynamic studies.[23]

Continued development of alternative, non-azole-based therapies for *Candida* species is needed.●

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