

Treatment Considerations in Vulvovaginal Candidiasis

The incidence of vulvovaginal candidiasis continues to rise. This paper outlines therapies that minimize the risk of side effects and drug interactions while maximizing compliance, plus specialized approaches for chronic recurrence, pregnancy, oral contraceptive use, diabetes, immunosuppression, and concomitant use of antibiotics and other drugs.

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In 1990, more than 13 million American women received prescriptions for treating vaginitis—the most common reason for visiting the gynecologist. (1) Vaginitis caused by yeast species accounts for approximately 40% of these cases, second only to bacterial vaginosis (45%). (2,3)

The incidence of vulvovaginal candidiasis (VVC) has increased dramatically in the past decade. In the United Kingdom, the incidence rose from 118 to 200 per 100,000 between 1975 and 1984, (4) and in the United States the number of prescriptions written to treat this condition doubled between 1980 and 1990. Up to 75% of women experience vaginal candidiasis in their lifetime (5)—approximately 40% to 50% of whom have a recurrence. (6) Fewer than 5% of women have chronic recurrences, however. (7)

Topical azoles remain the first line of VVC treatment, achieving mycologic and clinical cures with minimal systemic effects in 85% to 90% of episodic infections. Oral agents may be more convenient, but confer some risk of side effects and drug interactions. In addition, the proportion of nonalbican *Candida* infections caused by resistant strains may be on the rise.

MICROBIOLOGY

Candida is ubiquitous in nature, and is part of the normal flora of the mucocutaneous membranes. The overall carriage rate of *Candida* in healthy individuals is 80%, and it

can be isolated from the genital tract of about 20% of asymptomatic healthy women of childbearing age. (9) Approximately 80% to 95% of yeast vaginitis is caused by *C. albicans*. (2,3,9-11) Nonalbican *Candida* species (eg, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. krusei*, and *C. glabrata*)—although implicated less frequently in VVC (12)—are often more resistant to conventional therapy. (13)

Although the rate of VVC due to *C. albicans* decreased between 1980 and 1989 compared with 1970 to 1979, VVC from *C. glabrata*, *C. krusei*, and *C. tropicalis* increased. (14) The prevalence of nonalbicans VVC rose from 10% in 9 studies conducted in the 1970s to 21% in 7 studies conducted in the 1980s~ These data also show a rise in the incidence of *C. glabrata* from 4.6% to 6.7% and of *C. tropicalis* from 1.3% to 8.2%.¹⁴ Other series indicate that up to 35% of VVC cases are now caused by nonalbicans species. (13) The treatment implications here are substantial, because many antimycotics do not effectively eradicate nonalbicans strains.

RISK FACTORS

Risk factors for VVC include antibiotic use (particularly broad-spectrum agents), (15) pregnancy, poorly controlled diabetes mellitus, high-dose oral contraceptive (OC) use, (4,16) and immunosuppression due to human immunodeficiency virus (HIV) infection or chemotherapy. Attendance at a sexually transmitted disease (STD) clinic has also been

reported as a risk factor. (3,16) Wearing tight-fitting, synthetic-fiber clothing predisposes to vaginitis, (17-19) as do chemicals from products such as douches, deodorant sprays, and scented toilet paper. Other risk factors include local allergy or hypersensitivity reactions.

DIAGNOSIS

Evaluation of a patient with symptomatic vaginitis requires a thorough physical examination and medical history. Clinical findings and microscopic assessment must be considered in concert [Table 1]. The signs and symptoms of VVC are relatively non-specific; the most *Candida*-specific symptom is pruritus without discharge, which correctly predicts VVC in only 38% of patients. (3) Some patients have the typical "cottage-cheese" vaginal discharge, which may vary from watery to thick and usually does not have an odor.

Occasionally, patients complain of vaginal soreness and dyspareunia or external dysuria.

Physical examination may reveal vulvar erythema and swelling, often with discrete pustulopapular peripheral lesions. The cervix appears normal and the vagina erythematous. The adherence of secretions to the vaginal wall can be assessed during sampling. Figure 1 (20) depicts a rational approach to diagnosis in patients with vaginitis symptoms. Microscopic analysis lacks sensitivity, but is the best office tool for confirming VVC. (21) Direct microscopic examination of a wet-mount sample can rule out the presence of clue cells (bacterial vaginosis) and trichomonads, and may identify mycelia and/or budding yeast. Vaginal cultures are usually not necessary, and should be reserved for monitoring recurrences or determining whether recalcitrant infections are due to resistant organisms.

TREATMENT

Because many agents have comparable efficacy, selection depends on other factors--eg, the severity and duration of symptoms, the extent of inflammation, and the causative organism versus its known susceptibility pattern. Additional considerations include drug delivery to the infection site, safety issues, relative

resistance rates in cases requiring long-term therapy, and patient preferences to maximize compliance. A variety of agents is available to treat VVC [Table 2]. (22) The topical and oral azoles (imidazoles and triazoles) are used most often (23) and are generally effective, although there are some differences in efficacy against certain yeast species. Short-term eradication rates range from approximately 72% with clotrimazole to 95% or greater with tioconazole, fluconazole, miconazole, and terconazole. Long-term eradication rates (lack of resistance or recurrence) range from 57% with clotrimazole to 89% with tioconazole and terconazole [Table 3]. (24-28)

Among the azoles, tioconazole and terconazole appear to be the most active *in vitro*, with tioconazole demonstrating activity against *C albicans* as well as *C glabrata*, *C tropicalis*, *C krusei*, *C kefyr*, and *C parapsilosis*. By contrast, clotrimazole, miconazole, and butoconazole do not seem to be as active against *C glabrata* and *C tropicalis* as against *C albicans* (29) *C glabrata* seems to be less sensitive to agents such as ketoconazole and clotrimazole, (30) while fluconazole is less active against *C glabrata* and *C krusei* than against *C albicans*. (31) Use of the broadest-spectrum antifungal should result in higher over- all cure rates and less promotion of resistant yeasts.

The azoles achieve rapid therapeutic concentrations at the infection site, although the topical antifungals may provide quicker relief of irritation. In a study of a single 150-mg dose of oral fluconazole, the mean times to onset of relief and complete relief were 2 and 4 days, respectively, for both vaginal discharge and pruritus. (32) In another trial comparing terconazole 3-day vaginal suppositories with oral fluconazole, the mean number of days to onset of symptom relief was 2.4 for fluconazole and 1.8 for terconazole, and for complete symptom relief 6.08 and 6.60, respectively. (33)

The recent trend has been toward shorter treatment courses with higher antifungal doses, resulting in a number of 1-day regimens including oral fluconazole and tioconazole ointment, the only 1-day topical antifungal. In general, these shorter therapeutic courses

promote better compliance. (34) The higher-dose, single-use regimens actually provide prolonged therapy owing to persistence of effective drug concentrations in the vagina for 3 to 5 days. (35-37) Three days after applying a single 300-mg dose of tioconazole ointment, the mean concentration was approximately 100/ μ g/mL, as shown in Figure 2. (36) Use of single-dose oral fluconazole also resulted in persistence of therapeutic concentrations in the vagina for several days. (37) Furthermore, clinical results have demonstrated similar mycologic and clinical cure rates with single-dose and short-course (3- to 7-day) regimens using these agents. (38-41)

The current availability of over-the-counter (OTC) medications for VVC is a convenient option for many women, although the accuracy of self-diagnosis is questionable. For example, one study reported that only about 66% of patients correctly self-diagnosed VVC. Among the remainder, the correct diagnosis was actually trichomoniasis (30%), no infection (52%), (42) and other infection (18%). This finding underscores the importance of physician evaluation.

Among patients with infrequent VVC episodes, treatment failure is seldom due to drug resistance; mixed infections or lack of compliance is more likely. Compliance can be enhanced by choosing a single-dose regimen for patient convenience.

Resistance is a more important factor in patients with recurrent VVC, those who are taking long-term therapy, or those who are immunocompromised [Table 4]. (31,43-45) For example, *C glabrata* and *C krusei* have been implicated in VVC in women with HIV and neutropenic patients taking sustained fluconazole therapy, and these species have been associated with treatment failures. (31) The emergence of other, less common strains such as *C lambica* and *C lusitaniae*-which are inherently resistant to fluconazole-has been noted with empiric fluconazole use in neutropenic patients. (46)

SIDE EFFECTS

Both topical and oral azoles are generally well-tolerated. The most common side effects of topical treatment are headache and/or abdominal cramps (0.2% for both) and local burning, itching, or discomfort (0.9% to 6%)-rates similar to those often reported in patients receiving placebo. (47) Adverse effects reported most often with oral therapy are gastrointestinal (GI) symptoms in 5% to 12.5% of patients. (47)

Potentially more problematic adverse effects of oral therapy include isolated reports of angioedema and anaphylaxis. (48,49) Hepatotoxicity, although rare, has been reported with ketoconazole therapy. (50) A higher incidence of liver function abnormalities has also been noted with oral fluconazole as compared with a topical agent. (51) A recent report of congenital abnormalities in children of women taking multiple fluconazole doses during pregnancy raises concern about teratogenic effects. (52)

Clinically significant drug interactions can occur when certain oral azoles are taken with other medications [Table 5]. Serious arrhythmias--including torsades des pointes--have occurred in patients taking oral azoles together with nonsedating antihistamines (eg, astemizole and terfenadine); concurrent therapy with these agents should be avoided. Increased levels of therapeutic hormones, cyclosporine, anticoagulants, anticonvulsants, oral hypoglycemic agents, and theophylline can occur with concomitant oral antifungal use, but whether single-dose oral azoles can cause significant drug interactions with these agents is undocumented. Based on these factors, single-dose topical therapy may be preferable for routine treatment of episodic VVC.

SPECIAL CONSIDERATIONS

Chronic Recurrent Infection

Approximately 5% of women have chronic recurrent VVC, which is generally defined as four or more symptomatic episodes in 1 year that are confirmed microscopically or with cultures. (6,7) Causal factors usually cannot be identified, but may involve colonization of the oral, GI, and genital tracts and the presence of

azole-resistant strains of *C. albicans* or nonalbicans *Candida* species. Associated risks for recurrence include underlying illnesses (eg, HIV, diabetes). Use of chemotherapy or immunosuppressive therapy following transplantations also increases the risk of recurrences. Other contributing factors are similar to those noted for women with infrequent episodic candidiasis. Patients with recurrent infections must be evaluated by a physician and have the diagnosis confirmed microscopically and/or with cultures. In addition to other causative organisms, alternative diagnoses should be considered [Table 6].

Therapy should be individualized, and often involves trial and error. One approach is to treat the acute episode with a topical or oral agent until symptoms resolve, which may take 6 to 14 days, followed by maintenance therapy. Both intermittent and long-term continuous maintenance therapy may be beneficial, although the benefit may cease when treatment stops. Recurrence rates have been shown to decrease by 50% with intermittent therapy and by about 95% with daily maintenance therapy. Further, daily ketoconazole (100 mg/d for 6 months) was more effective for maintenance than monthly fluconazole, but 50% to 60% of ketoconazole patients have recurrences with cessation of treatment. (53,54) Weekly maintenance therapy with tioconazole for 6 weeks has been used successfully; boric acid douches and suppositories at 600 mg/d bid for 14 days and gentian violet have also been used. (55)

The issues of compliance and the increased potential for side effects and drug interactions with prolonged oral antifungal regimens are important considerations in choosing chronic therapy. Patients are more likely to comply with once-weekly regimens than with those requiring more frequent dosing.

Whether sexual partners of women with recurrent infections need treatment is controversial. For example, recurrence rates at 6 months have been reported as 65% and 71% among women whose sexual partners did and did not receive treatment, respectively, and recurrence rates at 1 year were 85% and 82%.

(56) Despite the lack of conclusive data, treating the sexual partner may prevent colonization of the penile skin and subsequent prostatic involvement.

Pregnancy

The incidence of candidiasis during pregnancy may be twice that in nonpregnant women, (33) and is highest during the third trimester. The increased hormone levels affect the glycogen content and normal flora, making the vaginal environment more conducive to *Candida* growth. Additionally, approximately 2% to 5% of women develop diabetes during pregnancy, further increasing their risk for candidiasis. (57)

Pregnant women presenting with VVC can be safely treated with topical agents after the first trimester. (58) Because of concern about fetal complications, pregnant women should not receive oral antifungal agents. In a retrospective UK study of 289 women given oral fluconazole during the months before or during pregnancy, no serious adverse effects were noted. (59) Recently, however, several cases of congenital abnormalities were reported in children of women who had received oral fluconazole during pregnancy—two of whom used daily chronic therapy throughout pregnancy. (52-60)

Oral Contraceptives

OCs with a high estrogen content (75 to 150 µg) have been implicated in increasing vaginal *Candida* colonization rates. The changes in the vaginal milieu are similar to those that occur during pregnancy. In one report⁶¹ the number of culture-positive infections doubled (18% vs 32%) in patients taking high-dose estrogen OCs. The progestin content may also play a role in increasing candidiasis risk. (62) With the newer low-dose OCs, however, this association has been significantly reduced.

Treatment of VVC in OC users is similar to that for nonusers, although longer-term therapy may be required. Because low-dose OCs are unlikely to contribute to candidal infection, discontinuation of OCs is not necessary for successful treatment. However, some anecdotal reports indicate that cessation of OC use occasionally resolves the infection in frustrating

cases. A growing body of evidence suggests that oral azole use in women taking OCs may increase the areas under the concentration-time curves of synthetic estrogen and progestin. (62) Although these alterations in hormone levels may not interfere with contraceptive efficacy, the clinical significance in terms of potential spotting and OC compliance is unknown.

Diabetes

Diabetes is a predisposing factor for VVC. Symptomatic infections are associated with poorly controlled diabetes, but most diabetic women do not have recurrent infections. (4) Hyperglycemia may impair several mechanisms of humoral host defense, including neutrophil adhesion, chemotaxis, and phagocytosis. In addition, vaginal epithelial cells have been found to bind *C albicans* with greater propensity in diabetics as compared with nondiabetics. (63,64)

Glucose control is important in managing diabetic women with VVC. Short courses of topical agents are the standard therapy. Oral agents are usually reserved for prophylaxis or treatment of systemic fungal infection, as they may interact with oral hypoglycemic drugs. The metabolic pathway of oral azoles involves the cytochrome P-450 enzyme system--the same system that metabolizes tolbutamide, glipizide, glyburide, and other hypoglycemic sulfonylurea agents. Concurrent administration may lead to increased activity of some sulfonylureas and hypoglycemia; specifically, both oral fluconazole and itraconazole have been associated with increased blood levels of sulfonylureas resulting in hypoglycemia, (65-72) and ketoconazole has been shown to decrease tolbutamide clearance, leading to increased circulating tolbutamide levels and ultimate hypoglycemia. (70,73-76)

Altered Immune States

Patients taking antibiotics, postoperative patients, and those who are immunosuppressed owing to anticancer or transplant therapy or HIV are at increased risk for symptomatic VVC. Their normal defense mechanisms may be diminished, and changes in the vaginal flora

may enhance *Candida* proliferation. Patients undergoing surgery often receive broad-spectrum antibiotics pre- or postoperatively; antibiotic use is known to raise *Candida* colonization in the vagina from a baseline of 10% to 30%. (77) Antimicrobials that suppress the normal protective vaginal lactobacilli (eg, penicillins, cephalosporins, tetracyclines) may be more likely to predispose to candidiasis than those that are relatively inactive at an acidic pH (eg, sulfonamides, erythromycin, metronidazole).

In general, patients taking antibiotics who develop symptoms of vulvovaginitis should have the diagnosis confirmed and receive treatment with single-dose topical or oral therapy. On the other hand, patients receiving long-term antibiotic therapy (eg, a tetracycline derivative for dermatologic acne) have a threefold increase in the rate of VVC. The physician who prescribes the antibiotic usually also prescribes short courses of antifungal therapy, and the patient consults a gynecologist only if the infection persists. In these cases, it is important to determine the causative organism(s) and possible reasons for persistence. If *C albicans* is confirmed, weekly or biweekly suppressive doses of an antifungal agent may be indicated if antibiotic therapy is to be continued.

The risk of candidiasis also increases in immunosuppressed patients because of cytotoxic chemotherapy or HIV infection. The duration of risk is directly related to the duration of neutropenia. Organ transplant patients often receive long-term steroid therapy, which also predisposes to candidiasis. Liver transplant patients typically have a high rate of serious systemic *Candida* infections, and routinely receive suppressive oral antifungal agents. Use of these drugs in a liver transplant patient with VVC but no systemic infection is inadvisable, though, because ketoconazole, fluconazole, and itraconazole can increase cyclosporine levels, leading to excessive immunosuppression or toxic side effects. (78) Furthermore, fluconazole prophylaxis in bone-marrow transplant patients increased the infection rate with *C krusei*. (79) Oral antimycotics should also be avoided in

granulocytopenic patients because of potential dissemination of resistant species from the GI tract. VVC in these patients should be treated with short courses of topical therapy. Prolonged topical therapy is appropriate for VVC patients on long-term steroid regimens and those who are immunocompromised.

PATIENT CONSIDERATIONS

In addition to the physical discomforts of VVC, many patients feel embarrassed about their illness and some may become depressed. Those with recurrent disease may even have associated sexual and marital problems. The increased time and costs of repeated medical visits can impose psychological and financial burdens as well. Physicians must take these factors into account, and provide counseling and assurance that VVC can be cured or at least controlled. Single-application therapies may decrease patient inconvenience and thus enhance compliance.

Patients must understand the terminology involved. If a language or cultural barrier exists,

other methods of communication must be used—such as asking the patient to point to the area that bothers her. Furthermore, to increase compliance, patients should participate in choosing a therapy and should be informed of possible side effects and drug interactions. It may also be useful to warn against any possibly harmful nontraditional alternatives involving use of strong herbal preparations or radical diets.

CONCLUSION

Many effective topical and oral treatments are available for VVC, all with demonstrated efficacy. This allows for flexibility with regard to issues such as potential adverse effects, drug interactions, safety in pregnancy, drug resistance, pathogen shift, and patient acceptance/compliance. In terms of each of these concerns, single-dose, long-acting topical agents offer an ideal choice for initial acute VVC therapy.

TABLES & FIGURES

Figure 1. Diagnostic evaluation of a patient with symptomatic vaginitis.*

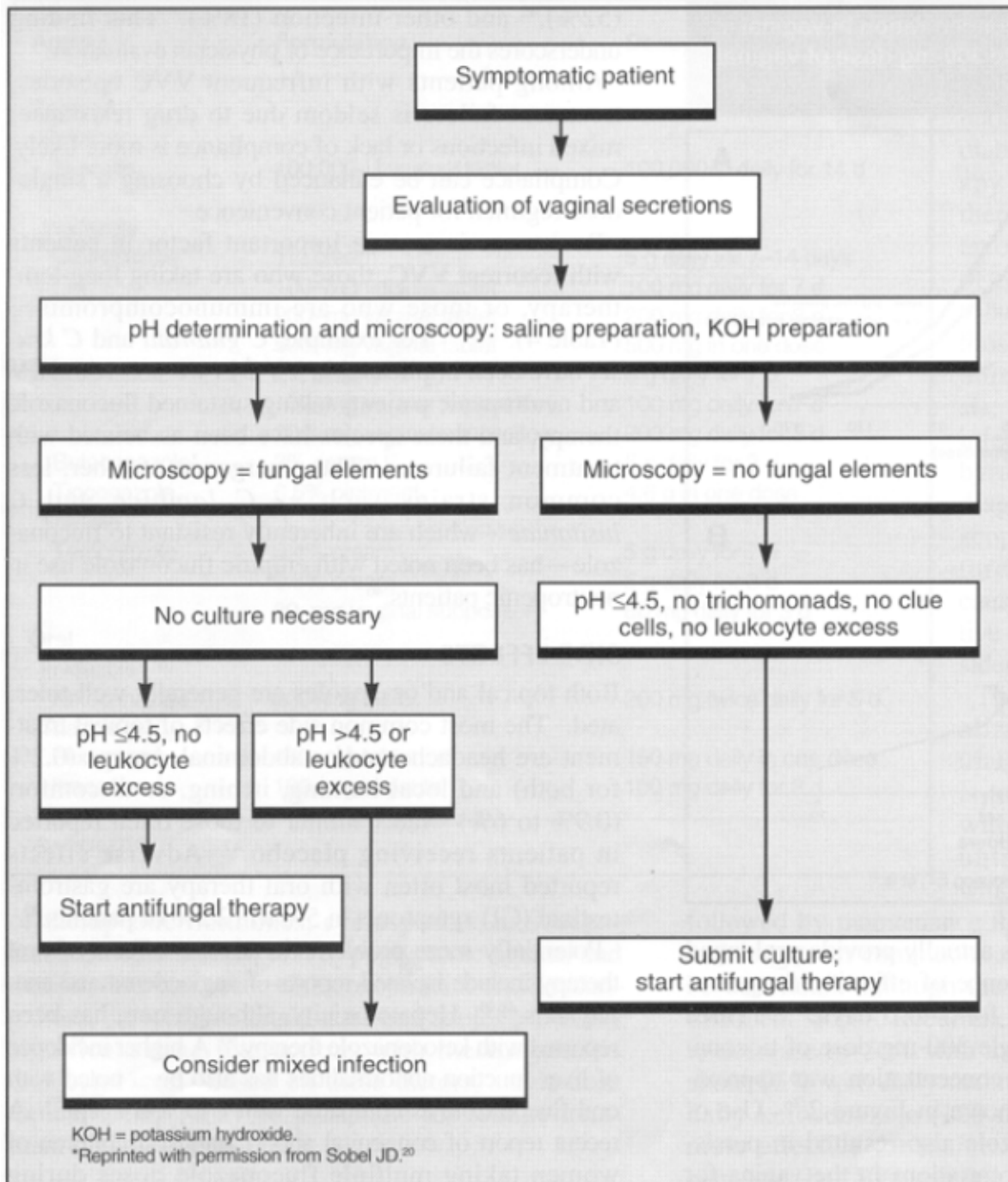


Figure 2. (A) Mean fluconazole concentration in plasma and vaginal secretions after a single oral dose (150 mg).*
(B) Mean tioconazole concentration in vaginal secretions after a single 300-mg dose of vaginal ointment (6.5%).³⁶

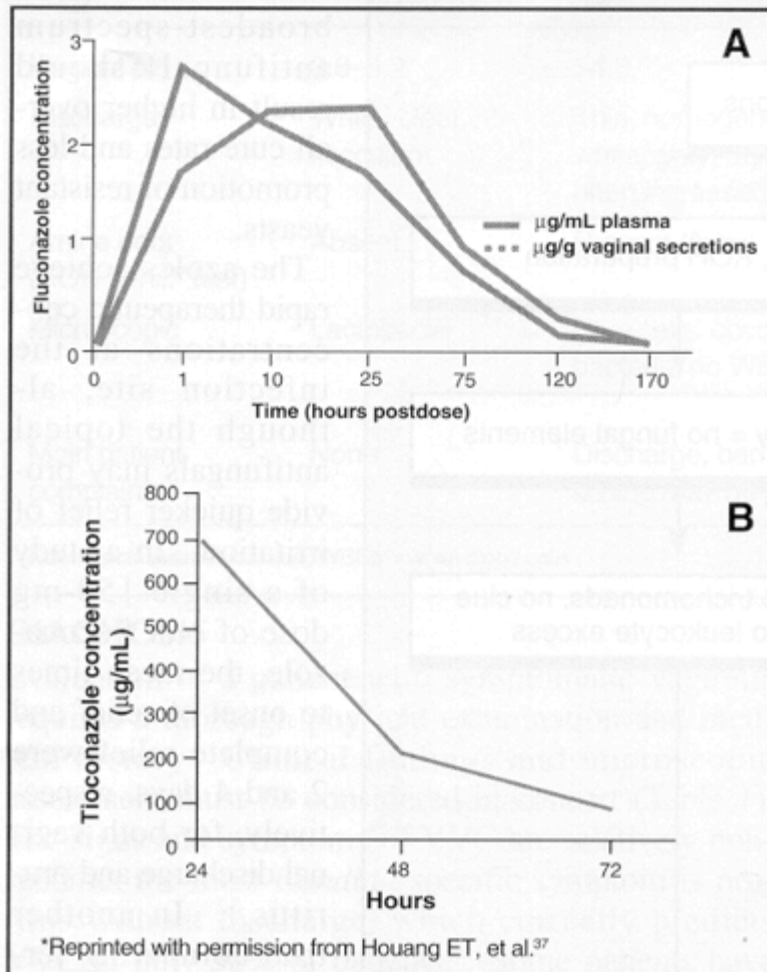


Table 1. Differential Diagnosis of Vaginal Infections

Diagnostic Criteria	Syndrome			
	Normal	Bacterial Vaginosis	Candidiasis	Trichomoniasis
Vaginal pH	3.8–4.2	>4.5	≥4.5 (usually)	>4.5
Discharge	White, clear, flocculent	Thin, homogeneous, white, grey, adherent, often increased	White, curdy, “cottage cheese”-like, sometimes increased	Yellow, green, frothy, adherent, increased
Amine odor (KOH “whiff” test)	Absent	Present (fishy)	Absent	Present (fishy) (not always)
Microscopic	Lactobacilli	Clue cells, coccoid bacteria, no WBCs	Mycelia, budding yeast, pseudohyphae with KOH prep	Trichomonad WBCs >10 hpf
Main patient complaints	None	Discharge, bad odor, itching may be present	Itching/burning, discharge	Frothy discharge, bad odor, pruritus

KOH = potassium hydroxide; WBCs = white blood cells

Table 2. Drug Formulations/Dosages for Treating VVC²²

Agent	Formulation	Dosage
Topical		
Polyene Nystatin	100,000-U vaginal tablet	100,000 U daily for 14 d
Imidazole Clotrimazole*	1% cream 100-mg vaginal tablet 200-mg vaginal tablet 500-mg vaginal tablet	5 g daily for 7–14 days 100 mg daily for 7 d 200 mg daily for 3 d 500 mg in one dose
Miconazole*	2% cream 100-mg vaginal suppository 200-mg vaginal suppository	5 g daily for 7 d 100 mg daily for 7 d 200 mg daily for 3 d
Butaconazole*	2% cream	5 g daily for 3 d
Tioconazole	6.5% ointment	4.6 g in one dose
Triazole Terconazole	0.4% cream 0.8% cream 80-mg vaginal suppository	5 g daily for 7 d 5 g daily for 3 d 80 mg daily for 3 d
Oral		
Imidazole Ketoconazole	200-mg tablet	200 mg twice daily for 5 d
Triazole Fluconazole	150-mg tablet	150 mg daily in one dose
Itraconazole	100-mg capsule	100 mg daily for 3 d

*Available OTC.

Table 3. Summary of Mycologic Eradication Achieved With Azole Antifungals²⁴⁻²⁸

Agent Tested	Dosage Used	Eradication Rates Reported (%)			
		No Pts	Short-term	No Pts	Long-term
Fluconazole	150 mg qd x 1	474	77-98	456	63-77
Ketoconazole	200 mg q12h x 5	72	82	74	77
Clotrimazole	100 mg qd x 7	176	72	165	57
	200 mg qd x 3	161	81	145	62
Miconazole	1200 mg qd x 1	50	96	50	82
Terconazole	40 mg qd x 3	115	95	114	89
Tioconazole	300 mg qd x 1	117	97	116	89

Table 4. Observed Resistance to Azole Antifungals^{27,44,45}

Organism	Antifungal Agent	Patient Population	Observations
<i>C krusei</i>	Fluconazole	Bone marrow transplant recipient; neutropenic patients; persistent vaginitis	Increased colonization and invasive disease following long-term prophylaxis or treatment. Decreased in vitro activity values reported in some cases
<i>C glabrata</i>	Fluconazole	Urinary tract infection; chronic vaginal candidiasis	In vitro resistance detected in these clinical failures
	Ketoconazole		In vitro resistance suggested
<i>C albicans</i>	Fluconazole	AIDS, oropharyngeal or esophageal candidiasis	Several studies show correlation with low in vitro activity and clinical resistance
	Ketoconazole	Patients with chronic conditions (eg, mucocutaneous candidiasis)	Resistance well documented following long-term therapy
<i>C tropicalis</i>	Ketoconazole; other imidazoles	Various clinical situations	Conflicting results; apparent clinical resistance in recurrent vaginitis cases
<i>Saccharomyces cerevisiae</i>	Fluconazole; short courses other azoles	Recurrent vulvovaginitis	Elevated MICs and clinical failure with fluconazole, clotrimazole, ketoconazole. Maintenance required; postinfection with <i>C glabrata</i> in some patients

MIC = minimum inhibitory concentration.

Table 5. Drug Interactions With Oral Azoles*

Drug	Effect When Taken With Azoles
Antacids	Decreased azole levels
Anticoagulants (coumarin and indanedione derivatives)	Increased anticoagulant levels
Astemizole	Arrhythmia, including <i>torsades des pointes</i>
Carbamazepine	Decreased itraconazole levels
Cimetidine	Increased itraconazole levels; decreased ketoconazole levels
Cyclosporine	Increased cyclosporine levels
Digoxin	Increased digoxin levels
Hydrochlorothiazide	Increased terconazole levels
Histamine H ₂ -receptor antagonists	Decreased absorption of itraconazole and ketoconazole
Hypoglycemics (oral)	Increased level of hypoglycemic agent
Isoniazid	Increased ketoconazole, itraconazole levels
Methylprednisolone	Increased plasma concentration of methylprednisolone
Omeprazole	Decreased absorption of itraconazole and ketoconazole
OCs	Decreased contraceptive levels
Phenytoin	Increased phenytoin levels; decreased itraconazole levels; increased or decreased ketoconazole levels
Rifampin	Decreased rifampin and azole levels
Terfenadine	Arrhythmia, including <i>torsades des pointes</i>
Theophylline	With fluconazole, increased level of theophylline, with ketoconazole, increased or decreased level of theophylline

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Table 6. Differential Diagnosis of Recurrent VVC

Yeast
 Bacterial vaginosis
Trichomonas vaginitis
 Allergic or hypersensitivity vulvitis
 Physiologic discharge
 Cyclic vulvitis
 Vulvar vestibulitis
 Dysesthetic vulvodynia
 Other STDs—gonorrhea, chlamydia, human papillomavirus
 Lichen sclerosis, hypertrophic dystrophy

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