

# **Recalcitrant and Recurrent Candidiasis and Bacterial Vaginosis**

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## **Learning Objectives**

At the end of this presentation, the participant will:

- Understand the various forms of candida vulvovaginitis
- Be comfortable diagnosing and treating recurrent/resistant yeast and bacterial vaginosis
- Realize that many treatments are not well studied

Conflicts of Interest:

Hope K. Haefner, MD has no conflicts of interest related to this topic. She is on the advisory board of Merck Co., Inc.

Vaginitis is a common problem seen daily in different care provider's offices. It accounts for over 10,000,000 office visits each year. The most prevalent infections are bacterial vaginosis (50%), candidiasis (30%) and trichomoniasis (20%). Less common causes of vaginitis include, foreign body, desquamative inflammatory vaginitis, and streptococcal vaginitis (very uncommon). Other conditions that cause vaginitis symptoms include collagen vascular disease, Behçet's syndrome, pemphigus and idiopathic conditions. The patient with chronic vaginitis is often frustrated, encounters difficulty in personal relationships, may suffer economic losses and at times, develops depression. A sense of hopelessness may exist.

### **NORMAL INHABITANTS OF THE LOWER GENITAL TRACT**

Lactobacillus	Klebsiella
Corynebacterium	Prevotella
Diphtheroids	Peptostreptococcus
Enterococcus	Eubacterium
Escherichia	Proteus enterobacteria
Staphylococcus	Fusobacterium
Streptococcus	Morganella bacteroides

### **Pelvic examination**

The pH of the vaginal discharge can easily and inexpensively be determined using pH strips. The pH paper should range from 3.5 to 7.0. The sample should be obtained approximately one third to midway down the lateral vaginal wall. It should not be contaminated with cervical mucous (pH=7.0). An aliquot of the diluted vaginal discharge should be examined microscopically (40x magnification). A drop or two of the discharge should be mixed with a drop of concentrated potassium hydroxide and whiffed to detect the presence of amines ("whiff test"). A positive test is detected by the presence of a fish-like odor which indicates the presence of bacterial vaginosis and/or anaerobes. The same specimen should be examined microscopically for the presence of fungal hyphae and/or budding yeast cells, which are resistant to alkali.

**Potential causes for elevated vaginal pH** include menses, heavy cervical mucus, semen, ruptured membranes, hypoestrogenism, trichomoniasis, bacterial vaginosis, foreign body with infection, Streptococcal vaginitis (group A) (rare), desquamative inflammatory vaginitis.

Examples of pH values follow (adapted from Linhares. Vaginal pH and Lactobacilli. Am J Obstet Gynecol 2011;204:120-1):

Gastic acid	1.5-1.0
Vinegar	2.9
Orange juice	3.5
Beer	4.5
Vaginal fluid (reprod age)	4.5
Milk	6.5
Saliva	6,5-7.0
Pure water	7.0
Semen	7.2-8.0
Blood	7.3-7.5
Seawater	7.7-8.3
Sidiom bicarbonate	8,4
Hand soap solution	9.0-10.0
Bleach	12.5

## **Vulvovaginal Candidiasis (VVC)**

The incidence of mycotic vulvovaginitis is rising dramatically in the United States. There are over 13 million cases of vulvovaginal candidiasis annually in the United States. Seventy-five percent of all women will have at least one episode of vulvovaginal candidiasis. About half of those infected experience more than one episode, and some patients suffer relapse and recurrence over a period of many years. Five percent of women with vulvovaginal candidiasis will develop recurrent episodes. *Candida albicans* most often causes infections in the United States. It is a dimorphic fungus that forms both spores and mycelia. It is followed in infection rate by *C. glabrata* and *C. tropicalis*. Over the past two decades, an increasing trend in the number of vaginal infections attributable to yeasts other than *Candida albicans* has emerged. If the common antifungal preparations used to treat yeast are ineffective, consideration should be given to culturing for a resistant strain of fungus. Recurrences are common. Predisposing factors include uncontrolled diabetes mellitus, steroid use, tight-fitting clothing/synthetic underwear, antibiotic use, increased frequency of coitus, "candy binges", and IUD use. Additionally, immune system alterations such as HIV/AIDS may be associated with a higher incidence and greater persistence of yeast infections. In patients with frequent yeast infections, consideration should be given to culturing specimens from sexual partners as well and giving appropriate antifungal therapy to them if positive cultures are obtained. Accurate diagnosis depends on culture techniques that will yield correct identification of the fungal pathogen(s).

### **Symptoms/Signs**

The main symptoms and signs of candidiasis are discharge, itching, burning/irritation, erythema, edema and excoriation. Rarely is vulvar candidiasis seen without concomitant vaginal candidiasis. Not all patients have symptoms of yeast infection. The incidence of asymptomatic fungal carriage in the vagina is quoted as 8-12 percent.

**Diagnosis** The acidity of vaginal secretions in candidiasis is usually within the pH range of 4.0-4.7. A wet mount preparation reveals spores of *C. albicans* which are uniform in size, isolated and almost always associated with hyphal-filaments. The spores of *C. glabrata* are of variable size (2-8 micrometers), spherical or ovoid, and usually smaller than a red cell. They are often grouped in clusters, although they may appear alone. Potassium hydroxide (10%-20%) preparation is often used to evaluate for yeast when they are not seen on saline prep. In this solution, pus cells and red blood cells dissolve. The branching, budding, and hyphal cell walls of *C. albicans* are easily visualized. Stained smears may also be used to diagnose *Candida*. Spores of *Candida* are strongly gram positive. The filaments are uniformly gram positive or have large gram positive granules.

Cultures should be obtained when symptoms are not explained on the wet prep or a patient presents with recurrent candidiasis. Some yeast forms may require as long as a month of incubation for detection (particularly with a small inoculum). Sabouraud's dextrose agar on modified Sabouraud's Difco mycobiologic media and Nickerson's media are satisfactory for growing *Candida* in an incubator or at room temperature, although identification of the species is not permitted. The most reliable differentiation of the species is provided by sugar fermentation reactions.

## Treatments

It is necessary to consider removal or improvement of predisposing factors in the treatment of candidiasis. Numerous antifungal preparations are available. If these are ineffective, then consideration should be given to culturing for a resistant strain of fungus. Such infections may require topical application of gentian violet solution or boric acid (per vagina). With failure of topical therapies, oral preparations should be considered. Treatments can be gauged by utilizing the mean inhibitory concentration (MIC) from recent studies. The lower the MIC, the more likely the antifungal will be effective. A current MIC table is available in the article by Richter et al.

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*.

Oral agents are convenient, but confer some risk of side effects and drug interactions.

<b>TOPICAL AGENTS FOR VULVOVAGINAL CANDIDA INFECTIONS (OVER THE COUNTER)</b>
Butoconazole
Clotrimazole
Clotrimazole Combination Packs (comes with a intravaginal medication in addition to a cream that can be used on the vulva.
Miconazole
Miconazole Combination Pack
Tioconazole

### Topical Prescription Medications for Vulvovaginal Candida Infections

DRUG	FORMULATION	DOSAGE
Butoconazole	2% cream	1 app per vagina x 1
Terconazole	80 mg vaginal sup	1 supp nightly for 3 days
	0.4% vaginal cream	1 app vaginally nightly for 7 days
	0.8% vaginal cream	1 app vaginally nightly for 3 days
Terconazole combination pack	80 mg vaginal supp	1 supp nightly x 3 nights Apply cream onto affected skin bid
Nystatin Powder	100,000 units/gram	Apply to vulva twice daily for 14 days

### Oral Fluconazole for Simple Candida Infection

fluconazole	150 mg oral tablet, one tablet in single dose
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### Other Oral azoles used for short term treatment

Drug	Dosage
Ketoconazole (Nizoral®)	400 mg po qd x 5 days
Itraconazole (Sporanox®)	200 mg bid x 1 day vs, 200 mg po qd x 3 days

## Prescription Medications for Recurrent Candida Infections

DRUG	FORMULATION	
Fluconazole	150 to 200 mg po q 72 hours x 3, then weekly.  If resistant to fluconazole, may consider itraconazole 100 mg po qd x 2 weeks, then twice weekly.	Consider stopping after 6 months and follow patient. Validated in multiple studies.  Consider stopping after 6 months and follow patient.

Or

7 day initial therapy with topical azole (Miconazole, clotrimazole, or butoconazole ) followed by a maintenance. Topical twice weekly. If that does not work other alternatives include 3 x per week or compounding.	All the topicals used for maintenance are not validated by studies.  Could consider compounding 1200 mg clotrimazole sup or 500 mg miconazole q week as a suppository  Only use itraconazole for maint if resistance Same allergy response as to fluconazole 100 mg daily	
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Or

Boric acid	600 mg per vagina qhs x 14, then twice weekly. NO DATA ON LONG TERM BORIC USE. Used for azole resistance, allergy; non albicans ( Fill an 0 gel capsule halfway to make a 600 mg dose).  ***NOT for oral use	
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	***Keep away from children No data on long term use.	
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Nystatin	100,000 units compounded into a suppository daily for 2 weeks, then twice weekly.	
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Patients who remain symptomatic should be recultured and reassessed for other diagnoses. Consider adding back antifungal when patient during antibiotic therapy. For this use 150 to 200 mg po fluconazole at start then q 7 days.

### Risk Factors for Recurrent Vulvovaginal Candidiasis

Antibiotic use	Receptive oral genital sex
Estrogen excess (OCP's , hormone replacement, local estrogens)	Sponge for contraception
Immune suppression (Lupus, HIV, corticosteroids)	Glucose excess (uncontrolled diabetes; refined sugar excess)
IUD use	Vulvar dermatoses (lichen sclerosus, eczema, atopic dermatitis)

Adapted from Sobel JD. Pathogenesis of recurrent vulvovaginal candidiasis. Current Infectious Disease Reports. 2002;4:514-9.

### Complicated Vulvovaginal Candidiasis

**Recurrent Vulvovaginal Candidiasis (RVVC)** (adapted from the 2010 CDC STD Treatment Guidelines)

To maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100 mg, 150 mg, or 200 mg oral dose of fluconazole every third day for a total of 3 doses (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen. Most patients with recurrent yeast prefer the oral antifungals. Side effects occur infrequently. Hepatotoxicity, such as is seen with ketoconazole, occurs less often with fluconazole, but is a known complication. In a patient with no known liver function abnormalities, consider checking liver function tests after 6 months of treatment with fluconazole.

**Maintenance Regimens** Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line of treatment. If this regimen is not feasible, topical treatments used intermittently as a maintenance regimen can be considered. Suppressing maintenance antifungal therapies are effective in reducing RVVC. However, 30%–50% of women will have recurrent disease after maintenance therapy is discontinued. *C. albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is usually not warranted for individual treatment guidance.

Routine treatment of sex partners is controversial. The CDC states that VVC is not usually acquired through sexual intercourse; no data support the treatment of sex partners. A minority of male sex partners might have balanitis, which is characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms. *C. albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is usually not warranted for individual treatment guidance.

**Fluconazole: Adverse effects**

- Nausea and vomiting in 3-4% (long term therapy)
- LFT monitoring consideration secondary to hepatotoxicity

>> chronic therapy >> AIDS patients

**Fluconazole: Drug-Drug Interaction**

- Drug history important with long term/chronic fluconazole therapy
- Not as much of a clinical concern with single dose therapy

**Drug interactions with long term fluconazole:**

Drug	Interaction
•warfarin (Coumadin®)	may increase PT
•cimetidine (Tagamet®)	20% lower Fluconazole peak
•oral contraceptives	decreased estradiol levels; no effect on break through bleeding, efficacy
•phenytoin (Dilantin®)	increased phenytoin serum levels
•rifampin levels	increased Fluconazole metabolism
•cyclosporine	increased levels of cyclosporine
•oral hypoglycemics	Hypoglycemia
•theophylline	increased theophylline levels
•terfenadine	?cardiac arrhythmias

## **Ketoconazole**

Ketoconazole traditionally has been used for long term therapy. Hepatotoxicity occurs and liver function tests need to be performed monthly.

## **Itraconazole**

Itraconazole is an azole that has been labeled in the United States only for histoplasmosis and blastomycosis. Studies in other countries indicate that it is quite effective in candidal and dermatophyte infections. A study evaluating a one-day monthly, intermittent itraconazole prophylaxis (two doses of 200 mg itraconazole 12 hours apart during the fourth or fifth day of the menstrual cycle) found a reduced rate of recurrence of yeast, but the beneficial effects of itraconazole were lost within a few months after cessation of prophylaxis. Liver function studies will also need monitoring with itraconazole.

Serious cardiac arrhythmias have occurred in patients taking oral azoles together with non-sedating antihistamines (e.g. astemizole and terfenadine).

**Other treatments for recurrent vulvovaginal candidiasis:** Consider suppression with a weekly intravaginal antifungal, for example, clotrimazole (Mycelex-G®), or butoconazole (Gynezone-1®), or tioconazole (Vagistat-1®).

**For irritation of yeast (like a diaper rash),** triamcinolone acetonide ointment 0.1 % plus Nystatin 100,000 units per gram to vulva bid x 14 days.

**Boric acid suppositories (per vagina)** Fill 0 gel capsule halfway (600 mg). For the initial treatment a 600 mg capsule is inserted **per vagina** daily for 14 days. For long term maintenance, insert **into vagina** twice weekly. (Especially useful with *Candida glabrata*)

**Gentian violet** 0.25% or 0.5% aqueous solution is applied at home daily or it may be given in the physician's office as a 1.0% solution (once weekly for up to three times). Permanent purple staining on clothing may occur. Some patients develop a vulvar irritation following application.

**5-flucytosine** This is a pyrimidine developed for use as an anticancer drug. Though not effective against cancer, it is fungicidal and is apparently deaminated within the yeast cell to 5-fluorouracil, which is incorporated into RNA and interferes with cell development. However, not all strains of *C. albicans* are susceptible, and drug resistance develops. It is very expensive currently.

- 500 mg / 5 grams compounded in hydrophilic cream base
- Insert 5 gram per vagina qhs x 14 nights

Horowitz has shown that, when used in this manner by women infected by imidazole-resistant strains of *C. tropicalis*, the drug is highly effective.

## **Vaginal candidiasis and pregnancy**

Many of the above agents are not to be used in pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women. Young and Jewell searched the Cochrane Pregnancy and childbirth Group register and concluded that topical imidazole was more effective than nystatin for treating symptomatic vaginal candidiasis in pregnancy. Treatments for seven days may be necessary.

## **Bacterial vaginosis.**

Various terms have existed throughout time for bacterial vaginosis. These include non-specific vaginitis, Hemophilus vaginitis, Corynebacterium vaginitis, Gardnerella vaginalis vaginitis, and anaerobic vaginosis. Bacterial vaginosis represents a complex change in vaginal flora. It is characterized by a reduction in the prevalence and concentration of hydrogen peroxide producing lactobacilli and an increase in the prevalence and concentration of Gardnerella vaginalis (found in 40% of women normally, found in 95% of women with bacterial vaginosis), mobiluncus species, Mycoplasma hominis, anaerobic gram negative rods belonging to the genera prevotella, porphyromonas, bacteroides, and peptostreptococcus species. Treatment of bacterial vaginosis (BV) is based on the understanding that it is not a disease but an unbalance of the vaginal ecosystem. This is an important concept because the imbalance is not due to a single bacterium or pathogen, but a disturbance in the ecosystem that allows the non-dominant symptom causing bacteria to become dominant.

The patient presents with a foul, "fishy" odor, more noticeable following intercourse and during menses. There is an increased or different vaginal discharge. Vulvar itching and/or irritation are present. The undergarments are stained at times.

Bacterial vaginosis may be diagnosed with other laboratory methods such as the use of DNA probes. These are expensive, but may be useful to practitioners unable to perform microscopy. Cultures have been used at times, but they are not useful since they are positive in 40-60% of asymptomatic females.

A new technique that includes nucleic acid probes for high concentrations of G. Vaginalis has become available (Affirm VPIII Microbial Identification Test).

## **Etiology of vaginal odor in BV**

- anaerobic bacteria concentrations increase 100-1000x with BV
  - anaerobic metabolism produces amines (cadaverine, putrescine, trimethylamine)
  - alkalinity volatilizes amines causing the sharp odor associated with BV

## Treatment (from 2010 CDC STD Treatment Guidelines)

### Recommended Regimens

**Metronidazole** 500 mg orally twice a day for 7 days\*

OR

**Metronidazole gel** 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days

OR

**Clindamycin cream** 2%, one full applicator (5 g) intravaginally at bedtime for 7 days†

\* Consuming alcohol should be avoided during treatment and for 24 hours thereafter.

† Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

### Alternative Regimens

**Tinidazole** 2 g orally once daily for 2 days

OR

**Tinidazole** 1 g orally once daily for 5 days

OR

**Clindamycin** 300 mg orally twice daily for 7 days

OR

**Clindamycin** ovules 100 mg intravaginally once at bedtime for 3 days

- Additional regimens include metronidazole (750-mg extended release tablets once daily for 7 days), or Clindamycin bioadhesive cream (Clindesse) 2% as a single vaginal dose of 5 grams of cream containing 100 mg of clindamycin phosphate. Data on the performance of these alternative regimens are limited.

Treatment of symptomatic women with bacterial vaginosis is indicated to reduce vaginal discharge and odor. During therapy with clindamycin cream, latex condoms can be affected and thus, should not be used.

Preoperative treatment prior to gynecologic procedures decreases the frequency of postoperative infectious complications.

Several studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV and restore normal flora. Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

## Treatment of pregnant women

Pregnant women with BV are at an increased risk of preterm birth. Screening of all pregnant women for BV is not recommended, given there is no evidence that screening and treatment of asymptomatic infection reduces the risk of preterm birth.

Symptomatic pregnant women with BV infection should be treated to relieve symptoms.

Asymptomatic women who are to undergo pregnancy termination should be treated.

### Follow-Up

Because recurrence of BV is not unusual, women should be advised to return for additional therapy if symptoms recur. A treatment regimen different from the original regimen may be used to treat recurrent disease. However, women with multiple recurrences should be managed in consultation with a specialist. One randomized trial for persistent BV indicated that metronidazole gel 0.75% twice per week for 6 months after completion of a recommended regimen was effective in maintaining a clinical cure for 6 months. (Sobel JD, Ferris D, Schwebke J, et al. Suppressive antibacterial therapy with 0.75% metronidazole vaginal gel to prevent recurrent bacterial vaginosis. *Am J Obstet Gynecol*;194:1283–9.)

### ***Allergy or Intolerance to the Recommended Therapy***

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole. Intravaginal metronidazole gel can be considered for patients who do not tolerate systemic metronidazole, but patients allergic to oral metronidazole should not be administered intravaginal metronidazole.

### **Recommended Regimens for Pregnant Women**

**Metronidazole** 500 mg orally twice a day for 7 days

OR

**Metronidazole** 250 mg orally three times a day for 7 days

OR

**Clindamycin** 300 mg orally twice a day for 7 days

30% of patients have BV recurrence within 3 months.

## **Treatment Guidelines for Recurrent/Resistant Bacterial Vaginosis**

Management of acute BV symptoms during relapse may require a longer treatment period of 10-14 days. Switch the agent. There is debate about treatment of partners. Most clinicians do not treat the partners.

Long term success with twice weekly suppression with intravaginal metronidazole has been reported (yeast infections did occur however).

Probiotics for bacterial vaginosis have been recommended. Studies are currently being performed to investigate their effectiveness.

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