

Vulvovaginitis: Screening for and Management of Trichomoniasis, Vulvovaginal Candidiasis, and Bacterial Vaginosis

This clinical practice guideline has been prepared by the Infectious Diseases Committee, reviewed by the CANPAGO and Family Physician Advisory Committees, and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all contributors.

Key words: bacterial vaginosis, yeast, candidiasis, trichomonas vaginalis, trichomoniasis, vaginitis, treatment

Abstract

Objective: To review the evidence and provide recommendations on screening for and management of vulvovaginal candidiasis, trichomoniasis, and bacterial vaginosis.

Outcomes: Outcomes evaluated include the efficacy of antibiotic treatment, cure rates for simple and complicated infections, and the implications of these conditions in pregnancy.

Evidence: Published literature was retrieved through searches of MEDLINE, EMBASE, CINAHL, and The Cochrane Library in June 2013 using appropriate controlled vocabulary (e.g., vaginitis, trichomoniasis, vaginal candidiasis) and key words (bacterial vaginosis, yeast, candidiasis, trichomonas vaginalis, trichomoniasis, vaginitis, treatment). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date limits, but results were limited to English or French language materials. Searches were updated on a regular basis and incorporated in the guideline to May 2014. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Summary Statements

1. Vulvovaginal candidiasis affects 75% of women at least once. Topical and oral antifungal azole medications are equally effective. (I)
2. Recurrent vulvovaginal candidiasis is defined as 4 or more episodes per year. (II-2)
3. *Trichomonas vaginalis* is a common non-viral sexually transmitted infection that is best detected by antigen testing using vaginal swabs collected and evaluated by immunoassay or nucleic acid amplification test. (II-2)
4. Cure rates are equal at up to 88% for trichomoniasis treated with oral metronidazole 2 g once or 500 mg twice daily for 7 days. Partner treatment, even without screening, enhances cure rates. (I-A)

J Obstet Gynaecol Can 2015;37(3):266–274

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in here has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁷⁶

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.⁷⁶

- Current evidence of the efficacy of alternative therapies for bacterial vaginosis (probiotics, vitamin C) is limited. (I)

Recommendations

- Following initial therapy, treatment success of recurrent vulvovaginal candidiasis is enhanced by maintenance of weekly oral fluconazole for up to 6 months. (II-2A)
- Symptomatic vulvovaginal candidiasis treated with topical azoles may require longer courses of therapy to be resolved. (I-A)
- Test of cure following treatment of trichomoniasis with oral metronidazole is not recommended. (I-D)
- Higher-dose therapy may be needed for treatment-resistant cases of trichomoniasis. (I-A)
- In pregnancy, treatment of symptomatic *Trichomonas vaginalis* with oral metronidazole is warranted for the prevention of preterm birth. (I-A)
- Bacterial vaginosis should be diagnosed using either clinical (Amsel's) or laboratory (Gram stain with objective scoring system) criteria. (II-2A)
- Symptomatic bacterial vaginosis should be treated with oral metronidazole 500 mg twice daily for 7 days. Alternatives include vaginal metronidazole gel and oral or vaginal clindamycin cream. (I-A)
- Longer courses of therapy for bacterial vaginosis are recommended for women with documented multiple recurrences. (I-A)

ABBREVIATIONS

HIV	human immunodeficiency virus
NAAT	nucleic acid amplification test
PHAC	Public Health Agency of Canada
STI	sexually transmitted infection
VVC	vulvovaginal candidiasis

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis is a very common condition that affects up to 75% of women at least once in their lifetime.¹ Risk factors for VVC include sexual activity, recent antibiotic use, pregnancy, and immunosuppression from such conditions as poorly controlled HIV infection or diabetes.^{2,3}

The Organisms

VVC is most often caused by *Candida albicans*⁴; however, other species of *Candida* such as *glabrata*, *parapsilosis*, and *tropicalis* are emerging.⁵

The main reservoir for *Candida* is thought to be the rectum, but vaginal colonization is also common. The factors associated with evolution from colonization to symptomatic infection are multiple and involve a combination of host susceptibility, host inflammatory responses, and *Candidal* virulence factors. Symptoms are thought to be caused by an overabundance of yeast and its penetration of vulvovaginal epithelial cells.⁶

The Disease

The signs and symptoms of uncomplicated VVC include a thick cottage-cheese-like discharge associated with vaginal and vulvar pruritus, pain, burning, erythema, and/or edema. External dysuria and dyspareunia may also occur.

Complicated VVC may be defined as that which is recurrent (4 or more episodes in a 12 month period), associated with severe symptoms, the result of a non-*albicans* species, or present in a compromised host.⁷ This condition is more

common in those with immunosuppression, diabetes, or both.⁸ Additional testing for HIV⁹ and diabetes may be warranted in these situations.

Diagnosis

The diagnosis of VVC requires pelvic examination. The combination of thick white discharge and vulvar pruritis is neither sensitive nor specific on its own for diagnosis.

Erythema and edema of vulvar and vaginal tissues, in conjunction with thick, white clumped vaginal discharge, are supportive of the diagnosis. The vaginal secretions of VVC have a pH < 4.5, and budding yeast and pseudohyphae may be seen on wet mount. Whiff test is negative and gram stain may reveal polymorphonuclear cells, budding yeast, and pseudohyphae.

When there is evidence of complicated VVC, collection of vaginal fluid for culture and yeast speciation may help direct therapy because there is an increased likelihood of non-albicans strains in such cases.¹⁰

Treatment

Treatment for VVC is necessary only in conjunction with symptoms. Identification of yeast on wet mount, gram stain/culture, or Pap screening in the absence of associated symptoms does not warrant therapy. Over 20% of women may have yeast as part of their natural vaginal microbiome and the majority will be asymptomatic.¹¹ Treatment and dosage options for uncomplicated, recurrent, and non-albicans VVC are summarized in Table 2.^{12–17}

Pregnancy

In pregnancy, VVC can be prolonged and associated with more severe symptoms, and resolution of symptoms typically requires longer courses of therapy. Only topical azoles are recommended in pregnancy. Treatment using external imidazole creams and intravaginal ovules for up to 14 days may be required. Repeat treatments may also be needed. Oral fluconazole should be avoided in pregnancy as it may increase the risk of tetralogy of Fallot.¹⁸ The safety of oral fluconazole in the second and third trimesters has not been investigated. Intravaginal boric acid has been associated with a greater than 2-fold increased risk of birth defects when used during the first 4 months of pregnancy,¹⁹ and should thus be avoided during this time.

Summary Statements

1. Vulvovaginal candidiasis affects 75% of women at least once. Topical and oral antifungal azole medications are equally effective. (I)
2. Recurrent vulvovaginal candidiasis is defined as 4 or more episodes per year. (II-2)

Recommendations

1. Following initial therapy, treatment success of recurrent vulvovaginal candidiasis is enhanced by maintenance of weekly oral fluconazole for up to 6 months. (II-2A)
2. Symptomatic vulvovaginal candidiasis treated with topical azoles may require longer courses of therapy to be resolved. (1-A)

TRICHOMONAS VAGINALIS

The Organism

T. vaginalis is an anaerobic parasitic protozoan flagellated organism that adheres to epithelial cells of the urogenital tract. For the most part, infection is limited to the genitourinary tract. With infection, the condition is referred to as Trichomoniasis.

The Disease

The prevalence of *T. vaginalis* in the United States is reported as 3.1% among women of reproductive age (14–49).²⁰ Globally, it is considered the most common non-viral STI, with an estimated 170 million cases reported annually.²¹ It is not a reportable disease in Canada, so precise data on Canadian prevalence is unavailable.

The symptoms associated with infection can be variable: 64% to 90% of infected people may have no symptoms,^{22,23} and infection, especially in those who are asymptomatic, may persist for months or years. Men tend to have fewer symptoms than women and can therefore serve as asymptomatic vectors for infection.²⁴ Men who are symptomatic may experience symptoms of urethritis: dysuria and a clear or mucopurulent discharge.²⁵ In women, the organism can be found in the vagina, cervix, bladder, or Bartholin, Skene, or periurethral glands.²⁶ Symptomatic women typically have a greatly increased volume of vaginal discharge; it may be malodorous, green or yellow in color, and frothy in appearance.²⁷ In addition, significant pruritis with vulvitis and vaginitis, dysuria, and dyspareunia may occur. Some may exhibit hemorrhagic spots (petechiae) on the genital mucosa, referred to as Colpitis macularis (strawberry cervix).²⁴

Diagnosis

Wet mount for microscopic visualization of the motile parasite has a sensitivity of up to 65%, and samples should be visualized within 10 minutes of collection to improve the likelihood of observing motility.²⁸

Culture of *T. vaginalis* has high specificity (almost 100%) but a lower sensitivity (as low as 75%) for diagnosis. Rapid transport to the laboratory is ideal to insure the viability of

Table 2. Treatment options for vulvovaginal candidiasis

Uncomplicated VVC*	Therapy	Medication	Dose
	Imidazole antifungals (over the counter)	Clotrimazole cream/ointment	1%: once daily × 7 days, or 2%: once daily × 3 days, or 10%: once only
		Insert/ovule/suppository	200 mg: once daily × 3 days or 500 mg: once only
		Miconazole cream/ointment	2%: once daily × 7 days, or 4%: once daily × 3 days
		Insert/ovule/suppository	100 mg: once daily × 7 days, or 400 mg: once daily × 3 days, or 1200 mg: once only
Triazole antifungals		Fluconazole (oral) (over the counter)	150 mg: once only
		Terconazole cream (prescription only)	0.4%: once daily × 7 days
Recurrent VVC†			
	Induction	Imidazole cream	10 to 14 days, as for uncomplicated VVC above ¹²
		Fluconazole (oral)	150 mg: 3 doses, 72 hours apart ¹¹
	Maintenance‡	Boric acid insert	300 to 600 mg daily × 14 days ¹³
		Clotrimazole insert	500 mg: once monthly × 6 months ¹⁵
		Fluconazole (oral)	150 mg: once weekly ¹¹
		Boric acid insert	300 mg daily × 5 days at the beginning of each menstrual cycle ¹³
		Ketoconazole (oral)§	100 mg once daily ¹⁴
Non-albicans VVC			
		Boric acid insert	300 to 600 mg nightly × 14
		Flucytosine cream	5 g once daily × 14 days
		Amphotericin B suppository	50 mg once daily × 14 days
		Nystatin suppository	100 000 units once daily for 3 to 6 months ¹

*These types of antifungal regimens are equally effective, with resolution of symptoms occurring in up to 90%.¹⁰

†Treatment for recurrent VVC requires induction therapy followed immediately by maintenance treatment.

‡Maintenance therapy should continue for 6 months. In cases of recurrence after completed therapy, induction and maintenance treatment should be repeated. Recurrence rates on maintenance treatment are low but can be as high as 50% in women off all therapy.

§Monitoring is recommended for rare hepatotoxicity with long-term use and drug interactions.

||Boric acid insert, flucytosine cream, and amphotericin B may be used in combination

the organism.²⁹ Although the organism may be detected on Papanicolaou screening tests, this is not considered diagnostic because of the test's low sensitivity for *T. vaginalis*.³⁰

Antigen testing

Immunoassay dipstick testing is available as a rapid antigen test with results available in 10 minutes. Sensitivity (82–95%) and specificity (97–100%) are both high.²⁹ NAATs are the most sensitive tests currently available for use with vaginal swabs. Urine and cervical swabs can also be used. Sensitivity and specificity for NAATs are both 95% to 100%.³¹

Because *T. vaginalis* is an STI, its diagnosis affords the opportunity to screen for other STIs.

Treatment

Treatment for *T. vaginalis* consists of oral metronidazole either 2 g once or 500 mg twice daily for 7 days. Cure rates

with either of these regimens are as high as 88%, and are even higher when sexual partners are simultaneously treated.³² Approximately 5% of *T. vaginalis* strains will be resistant to metronidazole. High dose and/or longer metronidazole therapy tends to be effective in these situations.³³ An alternate therapy for metronidazole-treatment-resistant cases is Tinidazole 2 g orally once.^{34,35} This is only available through Health Canada's Special Access to Drugs and Health Products Program.³⁶

Partner Treatment

The PHAC 2010 guidelines on STI do not recommend partner screening but do recommend treatment for all partners.⁷ Many men will be asymptomatic. Both patients and partners should be given the same type of treatment regimen. The 2010 Centres for Disease Control STI Guidelines suggest abstaining from intercourse until both

patients are treated and asymptomatic.³⁷ Test of cure is not recommended, but re-evaluation is suggested with symptom recurrence. There is an increased risk of HIV acquisition for both men and women with concomitant *T. vaginalis* infection, so it would be particularly important to screen and treat for this disease in HIV discordant couples.³⁸

Pregnancy

T. vaginalis infection in pregnancy has been associated with preterm delivery. If the patient is symptomatic and testing reveals infection, treatment is warranted. Screening and treatment for asymptomatic infection in women with a history of preterm birth or preterm premature rupture of membranes is controversial. Some studies have shown benefit and others have shown higher rates of preterm birth in the treated group.³⁹ The use of metronidazole in pregnancy is considered safe; numerous meta-analyses show no increased risk of teratogenic effects with metronidazole.⁴⁰ The recommended dose of metronidazole in pregnancy is the same as for non-pregnant women.

Side effects

Side effects of metronidazole may include nausea, vomiting, headache, insomnia, dizziness, drowsiness, rash, dry mouth, and metallic taste. A disulfiram reaction can occur if combined with alcohol. Avoidance of alcohol for at least one day after completing the treatment is recommended in the drug manufacturer's product monograph.

Summary Statements

- Trichomonas vaginalis* is a common non-viral sexually transmitted infection that is best detected by antigen testing using vaginal swabs collected and evaluated by immunoassay or nucleic acid amplification test. (II-2)
- Cure rates are equal at up to 88% for trichomoniasis treated with oral metronidazole 2 g once or 500 mg twice daily for 7 days. Partner treatment, even without screening, enhances cure rates. (I-A)

Recommendations

- Test of cure following treatment of trichomoniasis with oral metronidazole is not recommended. (I-D)
- Higher-dose therapy may be needed for treatment-resistant cases of trichomoniasis. (I-A)
- In pregnancy, treatment of symptomatic *Trichomonas vaginalis* with oral metronidazole is warranted for the prevention of preterm birth. (I-A)

BACTERIAL VAGINOSIS

The Organism

Normal vaginal flora consists of both aerobic and anaerobic bacteria, with *Lactobacillus* species being the predominant

microorganisms and accounting for greater than 95% of all bacteria present.^{41,42} Lactobacilli are believed to provide defense against infection in part by maintaining an acidic pH in the vagina and ensuring hydrogen peroxide is present in the environment. In contrast, bacterial vaginosis is a polymicrobial syndrome resulting in a decreased concentration of lactobacilli and an increase in pathogenic bacteria. There is no single organism whose presence confirms the diagnosis of bacterial vaginosis, but rather many different bacteria may be present, including *Gardnerella vaginalis*, *Mobiluncus* species, *Bacteroides* and *Prevotella* species, and *Mycoplasma* species.^{43,44}

The Disease

Bacterial vaginosis is the most common lower genital tract disorder among women of reproductive age, the most common cause of vaginitis in both pregnant and non-pregnant women, and the most prevalent cause of vaginal discharge and odour.^{45,46} Prevalence rates are similar in pregnant and non-pregnant women. It has been linked to many different obstetric and gynaecologic complications such as preterm labour and delivery, preterm premature rupture of membranes, spontaneous abortion, chorioamnionitis, postpartum endometritis, post-Caesarean delivery wound infections, postsurgical infections, and subclinical pelvic inflammatory disease.⁴⁷⁻⁵⁵

Several risk factors have been identified that increase the risk of acquisition of bacterial vaginosis. It is more common in black women,⁵⁶ women who smoke,⁵⁷ and women who use vaginal douches or intravaginal products.^{58,59} Although not currently considered an STI, bacterial vaginosis has been consistently associated with sexual activity. It is more common among women who are sexually active, and the risk seems to increase with both number of sexual partners and frequency of intercourse.^{60,61}

Diagnosis

Bacterial vaginosis can be diagnosed clinically and/or microbiologically. The clinical diagnostic criteria published in 1983 by Amsel et al., still in use today, recommend diagnosis of bacterial vaginosis if 3 of the 4 following signs are present⁶²: adherent and homogenous vaginal discharge; vaginal pH greater than 4.5; detection on saline wet mount of clue cells (vaginal epithelial cells with such a heavy coating of bacteria that the peripheral borders are obscured); and/or amine odour after the addition of potassium hydroxide (positive whiff test).

Gram stain of vaginal fluid is the most widely used and evaluated microbiologic method for the diagnosis of bacterial vaginosis. Most laboratories use an objective diagnostic scheme that quantifies the number of *Lactobacillus* morphotypes and pathogenic bacteria, resulting in a score

Table 3. Scoring system (0–10) for gram-stained vaginal smears

Score	<i>Lactobacillus</i> morphotypes	<i>Gardnerella</i> and <i>Bacteroides</i> spp. morphotypes	Curved gram-variable rods
0	4+	0	0
1	3+	1+	1+ or 2+
2	2+	2+	3+ or 4+
3	1+	3+	
4	0	4+	

Table 4. Recommended treatment regimens for bacterial vaginosis**Recommended**

Metronidazole 500 mg orally twice daily for 7 days

Metronidazole gel 0.75%, one applicator (5 g) intravaginally once daily for 5 days

Clindamycin cream 2%, one applicator (5 g) intravaginally once daily for 7 days

Alternatives

Metronidazole 2 g orally in a single dose

Clindamycin 300 mg orally twice daily for 7 days

that is used to determine whether the infection is present. The most commonly used system was developed by Nugent and colleagues and is known as the Nugent score (Table 3).⁶³ Bacterial vaginosis is diagnosed by a score of 7 or higher. A score of 4 to 6 is considered intermediate and a score of 0 to 3 is considered normal.

Treatment

Although bacterial vaginosis has been associated with adverse gynaecologic outcomes, there is no compelling evidence that treatment decreases the likelihood of these complications. Therefore, treatment is usually reserved for women with bothersome symptoms.

The treatments for bacterial vaginosis recommended in Canada in the PHAC's guidelines on STI are presented in Table 4.⁷ The first line therapy is oral metronidazole 500 mg twice daily for 1 week. Reported cure rates following therapy have ranged from 75% to 85% and do not differ between oral and vaginal metronidazole.^{64–66} Oral tinidazole has been studied as an alternative to metronidazole in trials in Europe and the United States. The evidence to date reveals similar cure rates with the possibility of a reduction in the number of doses required and in gastrointestinal side effects with tinidazole.^{67,68} This drug is not currently readily available in Canada.

Recurrent Bacterial Vaginosis

Unfortunately, recurrence rates following treatment for bacterial vaginosis have been high in many studies, with up to one third of treated women recurring within

3 months,⁶⁹ and with more women recurring the longer the length of follow-up.^{70,71} Before embarking on multiple courses of therapy, it is recommended to reconfirm the diagnosis. In women with documented recurrences, extending the course of therapy to continually suppress the growth of abnormal bacteria has been shown to be an effective strategy to decrease the likelihood of further recurrences. The first option is to use oral metronidazole 500 mg twice daily for 10 to 14 days. If this is not effective, the recommended therapy is metronidazole vaginal gel 0.75% one applicator (5 g) daily for 10 days, then 2 times per week for 3 to 6 months.^{7,72} This regimen results in a significant decrease in the likelihood of recurrences while on treatment and thereafter compared to placebo.⁷² There is also some evidence that condom use may decrease the likelihood of recurrence among sexually active women.⁴⁹

Recently there has been increasing interest in exploring the use of probiotics and other agents for the treatment of incident and recurrent bacterial vaginosis. Unfortunately very little literature exists to guide clinicians in the use of these products. There is one published study from China in which women with recurrent bacterial vaginosis were randomized to either daily vaginal probiotic use or placebo. Women in the probiotic group had lower recurrence rates than those in the placebo group.⁷³ Another study investigated the use of vaginal vitamin C tablets compared to placebo for the treatment of bacterial vaginosis. More women in the placebo group still had bacterial vaginosis at the end of the study period.⁷⁴ Unfortunately, in both

studies diagnosis was based on clinical (Amsel's) criteria rather than Nugent score or Gram stain, and the total length of follow-up in the vitamin C study was only 20 days. Until there is more published data from well-designed trials in this area, it is premature to make a judgement on the efficacy of these alternative therapies.

Pregnancy

Vaginal discharge is common in pregnancy and may be physiologic. In women with persistent discharge, screening for lower genital tract infections (vaginal and cervical) is recommended. If bacterial vaginosis is diagnosed in a symptomatic pregnant woman, treatment is indicated. The PHAC guidelines on STI recommend using metronidazole 500 mg orally twice daily for 7 days or clindamycin 300 mg orally twice daily for 7 days.⁷ Topical agents are not recommended. Treatment has relatively moderate rates of success with high rates of recurrence in some women.

For a detailed discussion of the implications of bacterial vaginosis in pregnancy and links to adverse pregnancy outcomes, including screening and treatment strategies in pregnant women, please see the SOGC Clinical Practice Guideline on the screening and management of bacterial vaginosis in pregnancy.⁷⁵

Summary Statements

5. Current evidence of the efficacy of alternative therapies for bacterial vaginosis (probiotics, vitamin C) is limited. (I)

Recommendations

6. Bacterial vaginosis should be diagnosed using either clinical (Amsel's) or laboratory (Gram stain with objective scoring system) criteria. (II-2A)
7. Symptomatic bacterial vaginosis should be treated with oral metronidazole 500 mg twice daily for 7 days. Alternatives include vaginal metronidazole gel and oral or vaginal clindamycin cream. (I-A)
8. Longer courses of therapy for bacterial vaginosis are recommended for women with documented multiple recurrences. (I-A)

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