

EVALUATION AND MANAGEMENT OF VAGINITIS

Betty Anne Johnson, M.D., Ph.D.
Professor of Medicine
Director, University Student Health Services
August, 2002

A. General Considerations

- Vaginitis symptoms are nonspecific and prompt 5-10 million office visits annually
- Self-diagnosis is unreliable
- Shotgun therapy is inappropriate; with a few simple diagnostic tests which can be performed in the office, accurate diagnosis is nearly always possible

B. Normal Vaginal Secretions

- Includes cervical mucous, exfoliating squamous epithelial cells from the vagina, transudated secretions through the vaginal wall
- Normal secretions are:
 - Colorless
 - Clear or white
 - Viscous, homogeneous or somewhat flocculent
 - No pooling noted on exam
- Rare polyps are present
- pH is low (<4.5); may be higher in prepubertal girls and in post-menopausal women
- Lactobacilli dominate but up to 10 other bacterial species can be cultured including
 - staph epi
 - gardnerella
 - strep (Group B strep is present in about 15-20% of women)
 - coliforms
 - bacteroides.
- Nonbacterial microorganisms are present in sexually active women including
 - Candida albicans (5-10%)
 - Mycoplasma hominis (20-50%)
 - Ureaplasma urealyticum (50-70%)

REMEMBER! The vaginal flora is a dynamic ecosystem that constantly changes. Lower genital tract infections in women are not caused by a single specific organism but rather result from quantitative changes in existing flora.

C. Types of Vaginitis

- Four etiologies are common
 - Bacterial Vaginosis (BV)
 - Vulvovaginal candidiasis (VVC)
 - Trichomonas vaginitis (TV)
 - Atrophic vaginitis (AV)

D. Bacterial Vaginosis

General Considerations:

- Most common vaginal discharge
 - 17-19% in family planning clinics or student health services
 - 24-37% in STD clinics
 - 10-29% among pregnant women
- 50% of women with BV may not report symptoms
- Risk factors include having multiple sex partners, douching, and lack of vaginal lactobacilli
- Occurs when there is overgrowth of non-lactobacillus anaerobic bacteria which replaces the endogenous flora
- *Gardnerella vaginalis* is often present but is a normal commensal as well; overgrowth distinguishes the symptomatic from the asymptomatic woman
- Lack of inflammation; therefore “vaginosis” as opposed to “vaginitis”
- Whether sexually transmitted is controversial; treatment of partners has not increased the cure rate for BV

Clinical Implications and Morbidity

BV is associated with an increased risk of several conditions:

- Cuff cellulitis following hysterectomy
- Endometritis and wound infection after CS
- Postabortion PID
- Plasma cell endometritis

It is estimated that 15-20% of pregnant women have BV. Pregnant women have several risks:

- Amniotic fluid infection
- Clinical chorioamnionitis
- Postpartum endometritis
- Premature rupture of membranes
- Preterm delivery

Diagnosis

Diagnosis is remarkably simple and useful in clinical practice for the clinicians trained in clinical microscopy. Otherwise, overdiagnosis is common.

- Homogeneous vaginal discharge (color and amount may vary but often off-white, thin); vaginal walls and cervix are not inflamed
- Malodorous “fishy” smell, which may increase after sex (semen has a pH of 7 and causes dissociation of amines) or after addition of KOH to a sample of vaginal secretions (+Whiff test); most powerful single predictor!
- Vaginal pH > 4.5; pH in BV usually is 5-5.5. Dip a pH strip into vaginal secretions; avoid cervical secretions, which have a higher pH. pH alone is the most effective test to identify women who do NOT have BV
- Presence of “clue cells” (Mix 1 drop of discharge with 1-2 drops of saline. Under hi-dry, > 20% of the epithelial cells will have a granular appearance and indistinct cell margins from adherence from bacteria.) PMNs are not usually present unless there is a mixed infection
- Newer methods of diagnosis include a DNA probe based test for high concentrations of *G. vaginalis* (Affirm™ VPIII, Becton Dickinson). Pap smear has low sensitivity.

Treatment

- Single dose metronidazole effective (85-95% cure rate) but higher recurrence rate than 1 wk Rx
- Topical therapy is as effective as oral therapy but more expensive
- Recurrence rates are high within 3 months probably not from antibiotic failure but from failure to establish the normal protective vaginal flora dominated by lactobacillus

Treatment Regimens for BV

Drug	Dosage
<i>Oral Treatment</i>	
Metronidazole (Flagyl)	500 mg bid x 7 d
Metronidazole (Flagyl)	2 gm orally, single dose
Clindamycin (Cleocin)	300 mg bid x 7 d
<i>Topical Treatment</i>	
Clindamycin cream 2% vaginal	5 g q hs x 7d
Metronidazole vaginal gel (Metrogel vaginal) 0.75%	5 g bid x 5 d
Clindamycin ovules 100 g	100 g qhs x 3 d

BV in Pregnancy

- Because treatment of BV in high risk women (women who have previously delivered a premature infant) might reduce adverse pregnancy outcomes, the CDC is recommending that such women be screened and treated at the first prenatal visit. The US Preventive Services Task Force has concluded that there is insufficient evidence to recommend for or against screening high-risk pregnant women for BV and recommends against screening average-risk asx pregnant pts.
- Recommended treatment regimens during pregnancy include lower doses to minimize exposure of the fetus:

Treatment Regimens for BV During Pregnancy

Drug	Dosage
Metronidazole	250 mg po tid x 7d
Clindamycin+	300 mg bid x 7 d

+ The use of clindamycin vaginal cream during pregnancy has been associated with preterm delivery and is not recommended.

- Low-risk pregnant women (those who previously have not had a premature delivery) who have symptomatic BV should be treated to relieve symptoms. All of the above regimens may be used or alternatively, metronidazole gel 0.75%, one full applicator (5 grams) intravaginally bid for 5 days

E. Vulvovaginal Candidiasis (VVC)

General Considerations

- Caused by *C. albicans* and *C. glabrata*, both of which are part of the normal flora in up to 20% of asx women. *C. albicans* is responsible for 80-95% of fungal vaginitis. *C. glabrata* (formerly *Torulopsis*) accounts for 3-16%, causing milder sx but more resistant to Rx.
- The vaginal epithelium of some women is relatively resistant to adherence from candida whereas others show increased avidity.
- Not considered an STD but episodes may be linked to receptive orogenital sex
- Less common in postmenopausal women but by age 25, nearly half of all college women will have had at least one episode of physician-diagnosed vulvovaginal candidiasis
- Predisposing factors:
 - Pregnancy
 - Diabetes
 - Recent antibiotic use
 - OCP's
 - Steroid use
 - Immunosuppressants
 - AIDS

Diagnosis

- “Thrush-like” vaginal discharge with white clumps adherent to the vaginal wall (“cottage-cheese” appearance) but discharge can be variable
- vulva may be indurated and edematous with fissures or maceration present
- rash in the intertriginous area of the vulva is common as well as satellite lesions
- pH < 4.5 (This is a normal pH).
- Usually no odor present
- Gram stain or KOH prep (1 drop of vaginal discharge mixed with 1 drop of 10% potassium hydroxide) reveals fungal elements (pseudohyphae) when examined under hi-dry. KOH prep fails to detect 30-50% of culture-positive infections. Gram stain improves on the sensitivity of the microscopic exam. Clinician must be able to recognize blastospores in the absence of mycelia to diagnose non-*C albicans* species such as *C glabrata*.

Treatment

Of the **oral agents**, fluconazole is by far the most effective and reaches highest concentrations in vaginal fluid. Many women prefer oral agents over topicals.

- The long half-life of fluconazole allows single-dose administration; for severe cases, another dose may be administered in 4-5 days.
- Fluconazole is eliminated primarily unchanged through the kidneys
- Fluconazole may increase the concentration of oral hypoglycemics, cyclosporine, warfarin and phenytoin. Drug interactions may also occur with astemizole, calcium channel antagonists, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.
- No orals are approved for use during pregnancy

Topicals are unlikely to cause drug interactions because very little is absorbed.

- Cure rates are 80-90%.
- Principal side-effects of topicals include local burning, itching, stinging and irritation.
- Of the topicals, the most effective during **pregnancy** are butoconazole, clotrimazole, miconazole, and terconazole. Many experts recommend 7 days of therapy during pregnancy.

Treatment Regimens for Vulvovaginal Candidiasis

Drug	Dosage
<i>Oral Treatment</i>	
Fluconazole (Diflucan)	150 mg po x 1
<i>Topical Treatment</i>	
Miconazole vaginal supp*	200 mg qhs x 3 or 100 mg qhs x 7
Miconazole 2% cream+ *(Monistat-7)	1 applicator vaginally qhs x 7
Miconazole vaginal supp and topical cream *(Monistat Dual Pack)	1 supp vag qhs x 3; apply cream to vulva bid
Clotrimazole+ (Gyne-Lotrimin, Mycelex)	100 mg vag tablets qhs x 7 or 2 x 100 mg vag tablets qhs x 3; 500 mg tablet vag x 1
Clotrimazole 1% cream *(Lotrimin)	1 applicatorful vag qhs x 7-14 d
Butoconazole+* 2% cream (Femstat)	1 applicatorful vag qhs x 3
Butoconazole 2% cream 5 gm (Butaconazole 1-sustained release)	single intravaginal application
Terconazole cream +(Terazol)	0.4% cream, 1 applicatorful vag qhs x 7; 0.8% cream, 1 applicatorful vag qhs x 3
Terconazole supp 80 mg (Terazol)	1 supp vag qhs x 3
Tioconazole* (Vagistat)	6.5% ointment, 5 g in a single dose

+ Approved for use during pregnancy; many experts recommend 7 day therapy during pregnancy

* OTC

Complicated Vulvovaginal Candidiasis includes:

- Recurrent vulvovaginal candidiasis
- Severe vulvovaginal candidiasis
- Non-albicans vulvovaginal candidiasis
- Compromised host
- Pregnancy

Recurrent vulvovaginal candidiasis (RVVC) is defined as 4 or more mycologically proven symptomatic episodes within 12 months

- affects about 5% of women

- There is good evidence for an association between RVVC and receptive oral sex¹, oral contraceptives² and nonsecretor status which facilitates vaginal yeast colonization³
- There is little scientific evidence for the role of the following in recurrent episodes:
 - Diet or clothing
 - Deficiency in vaginal lactobacilli
 - Use of menstrual protection and feminine hygiene products
- Our understanding of RVVC is now confounded by the growing use of OTC antifungal treatments. In 1991 alone, American women spent more than \$100 million on OTC antifungals!.
- Often the patient with RVVC will have both vulvovaginal candidiasis as well as another dermatologic disorder, the most common of which is **chronic vulvar contact dermatitis**. In this disorder, the patient complains of vulvar burning when antifungals, hormones, steroid creams or other medications are applied to the vulva. Frequent application of petrolatum (vaseline jelly) may hasten resolution of contact dermatitis symptoms after stopping the offending agent.
- Fungal culture should be done before instituting intensive or maintenance therapy.
- Women with RVVC may require higher doses of drugs for longer periods of time than previously believed. The optimal treatment regimen for RVVC has not been established but the CDC recommends a 10-14 d intensive course of topicals (or an oral dose of fluconazole repeated 3 days later) followed by at least 6 months of maintenance therapy. Maintenance therapy with ketoconazole 100 mg day for ≤ 6 months has been shown to reduce the frequency of RVVC episodes. Other possible maintenance regimens follow:
 - Itraconazole 100 mg/d or 400 mg dose once monthly (1 in 10,000 women will develop hepatotoxicity; pts receiving long-term ketoconazole should be monitored for toxicity.
 - Fluconazole 100-150 mg once weekly
 - Clotrimazole 500 mg vaginal suppositories once weekly

Severe vulvovaginal candidiasis (extensive vulvar erythema, edema, excoriation, and fissure formation)

- Lower clinical response to short course treatment
- Use 7-14 d of topical azole or 150 mg fluconazole repeated in 72 hrs

Non-albicans vulvovaginal candidiasis

- Longer duration of treatment is recommended (7-14d)
- Intravaginal boric acid 600 mg bid for 2 weeks may be tried for resistant non-*C albicans* infection. Boric acid is contraindicated in pregnancy.

¹ Hellberg D, Zdolsek B, Nilsson S, Mardh PA. Sexual behavior of women with repeated episodes of vulvovaginal candidiasis. *Eur. J Epidemiol.* 1995; 11:575-579.

² Spinillo A, Carratta L, Pioli G, et.al. Impact of oral contraception on vulvovaginal candidiasis. *Contraception.* 1995; 51:292-297.

³ Hilton E, Chandrasekaran V, Rindos P, Isenberg HD. Association of recurrent candidal vaginitis with inheritance of Lewis blood group antigens. *J. Infect Dis* 1995; 172:1616-19.

Compromised host: use longer courses of treatment

Pregnancy: Only topical azole therapies, applied for 7 days, are recommended in pregnant women

HIV-infection: Symptomatic vulvovaginal candidiasis is more common in HIV infected women.

- Use of azole therapies is associated with isolation of non-albicans species.
- Therapy should in general be similar to that of non-HIV infected women
- Long-term prophylactic therapy with fluconazole at 200 mg weekly has been effective in reducing colonization and symptomatic vulvovaginal candidiasis but is not recommended for routine primary prophylaxis in HIV-infected women.

F. Trichomonas Vaginitis (TV)

General Considerations

- Protozoal infection found only in the GU tract of men and women, esp bladder, urethra, prostate, vagina, periurethral glands, Bartholin's glands.
- Attaches to epithelial cells
- Causes inflammation
- Extracellular parasite, flagellated which causes it to move in a jerky motion
- Decreasing in prevalence in most industrialized nations
- Postmenopausal women are often asx as they have poorly glyconated squamous epithelium which does not promote the growth of trich
- Sexually transmitted with a high transmission rate
- Prevalence of trich infection correlates with sexual activity and is highest in women with multiple partners
- Most female partners of infected men and 30-80% of male partners of infected women harbor trich
- Men may spontaneously clear trich infection within 2 weeks probably secondary to poor attachment of trich to urethral cells

Diagnosis

- Half of infected women are asx but the rest complain of vaginal discharge, itching, dyspareunia and/or dysuria
- Sx usually sudden and severe in onset
- Vaginal discharge may be frothy and profuse
- Trich is invasive so small petechiae may be present on the cervix ("strawberry spots")
- Diagnosis requires identification of MOTILE organisms on wet prep (one drop of vaginal secretions mixed with 1-2 drops of normal saline; do not let the slide dry)

out; examine under low to hi-dry power) Trich are slightly larger than a WBC and if not moving, cannot be distinguished from a WBC. Sensitivity of direct microscopy is 60-75% but the specificity approaches 100%. PAP smears have a similar sensitivity but a lower specificity.

- Wet prep shows lots of PMNs
- Vaginal secretions have pH > 4.5
- Detection of trich in men requires prostatic massage followed by collection of first morning urine for microscopic examination. Because this is difficult, we often treat sexual partners of infected women presumptively.
- Several new rapid diagnostic kits using DNA probes and monoclonal antibodies are available with a sensitivity of 90% and a specificity of 99.8%

Treatment

Treatment Regimens for Trichomonas

Drug	Dosage
Flagyl	2 grams all at once
Flagyl	500 mg bid x 7 d
<i>For Treatment Failures</i>	
Flagyl	500 mg bid x 7 d
Flagyl	2 grams q d x 3-5 d

- Cure rates of 90-95% are common with the std regimens.
- Topicals including metronidazole gel are unlikely to work as they do not achieve therapeutic levels in the urethra or perivaginal glands
- For patients who do not respond to treatment and in whom reinfection has been excluded, the CDC recommends consultation with them (770-488-4115; website: <http://www.cdc.gov/std/>). Evaluation of such cases should include determination of the susceptibility of the organism to metronidazole.
- Patients allergic to oral metronidazole should not receive vaginal metronidazole.
- Metronidazole is the drug of choice for treatment in pregnancy. The CDC recommends 2 grams metronidazole as a single dose during pregnancy.

G. Atrophic Vaginitis (AV)

General Considerations

- ◆ Occurs in women undergoing either natural or surgical menopause
- ◆ Vaginal epithelium becomes thin and atrophic when deprived of estrogen; vaginal pH increases and overgrowth of nonacidophilic coliforms occurs with the disappearance of lactobacilli
- ◆ Clinically significant atrophic vaginitis is uncommon

Diagnosis

- ◆ Symptoms may include vaginal soreness, postcoital burning, dyspareunia, and occasional spotting
- ◆ Vaginal mucosa is thin, may be diffusely red with occasional petechiae or ecchymoses with few or no vaginal folds
- ◆ Discharge may be serosanguineous or watery
- ◆ Discharge pH 5-7
- ◆ Wet prep may show PMNs asso with small, rounded parabasal epithelial cells.
- ◆ Lactobacilli replaced by GNR

Treatment

- ◆ Topical estrogen therapy (nightly use of ½ applicator for 1-2 weeks will alleviate sx; then can reduce dose to once weekly or monthly); one product is dienestrol vaginal cream 0.01%.
- ◆ Oral hormone replacement therapy will also alleviate sx.
- ◆ Other possibilities include agents which restore vaginal moisture: Replens, Atroglide, Lubrin vaginal suppositories

References:

Cleveland, A. Vaginitis: finding the cause prevents treatment failure. *Cleveland Clinic J of Medicine* 2000;67:634-646

CDC 2002 Sexually Transmitted Diseases Treatment Guidelines, *MMWR Weekly Report*, 2002;51 (RR-6), 1-84

National Association of Managed Care Physician Roundtable Highlights.
Vulvovaginitis: A Practice Protocol for the Managed Care Clinician. January, 1996.

Majeroni B. Bacterial Vaginosis: An Update. *American Family Physician* 1998; 57:1285-1289.

Sobel J, Vulvovaginal Candidiasis: A Contemporary Approach to Recognition and Management. Continuing Medical Education Activity, Fall, 1997. Wayne State University

Sobel J. Vaginitis. *NEJM* 1997; 337:1896-1903.

US Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy: recommendations and rationale. *American Family Physician* 2002;65:1147-1150

Differential Diagnosis of Vaginitis¹

Variable	Normal	Vulvovaginal Candidiasis	Bacterial Vaginosis²	Trichomonas Vaginitis	Atrophic Vaginitis
Symptoms	None or mild, transient	Itching, soreness, change in discharge, dyspareunia	Malodorous discharge, no dyspareunia	Malodorous, purulent discharge; dyspareunia	Dyspareunia, vaginal dryness
Signs		Vulvar erythema, edema, fissures; adherent discharge	Discharge is off-white, thin, homogeneous	Vestibular and vaginal thinning	
PH	4.0-4.5	4.0-4.5	>4.5	5-6.0	>6.0
Whiff test	Negative	Negative	Positive (70-80%)	Often positive	Negative
Saline Microscopy	PMN:EC ratio <1.0; rods dominate; Squames +++	PMN:EC ratio <1; rods dominate; squames +++; pseudohyphae evident in 40%	PMN:EC <1; increased coccobacilli; clue cells in > 90%	PMN ++++; mixed flora; motile trich in 60%	PMN + to ++; loss of rods; increased cocci and coliforms; parabasal cells
10% KOH	Negative	Pseudohyphae 70%	Negative	Negative	Negative
Misc		Culture if in doubt			
Differential Diagnosis	Physiologic leukorrhea	Contact irritant or allergic vulvitis, chemical irritation, vulvodynia		Purulent vaginitis, desquamative inflammatory vaginitis, atrophic vaginitis plus secondary infection, lichen planus	

¹Adapted from Sobel J, *NEJM*, 1997; 337:1898;
 PMN denotes polymorphonuclear leukocytes; EC denotes epithelial cells

² To diagnose BV, must have 3 of 4 clinical signs: homogeneous discharge, a positive whiff test, pH .4.5 and/or presence of clue cells

