Vaginal Discharge Syndromes: Vaginal Infections and Cervicitis

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Cervical Anatomy and Terminology

- Ectocervix
- Endocervix

Ectopy (“Ectropion”, “Erosion”)
- Physiologic ectopy: Migration of endocervical mucosa onto the ectocervix ~menarche
  - Usually regresses age 17-20
  - Can recur during pregnancy or hormonal contraception
  - Probably one reason *C. trachomatis* is so strongly related to young age in women
  - Regression can generate nabothian cysts
- Pathologic ectopy: Edema due to inflammation (cervicitis) results in eversion (“edematous ectopy”)

- Vagina has no mucus-secreting glands; presence of mucus in vaginal secretions denotes cervical origin
Symptoms of Cervicitis

- Most cases are subclinical, either truly asymptomatic with minor variations in quantity or quality of vaginal secretions
- Increased vaginal discharge
  - Variable color and staining
  - Little or no odor
- Dysuria (actually represents concomitant urethritis)
- Abnormal bleeding
  - Usually scant
  - Often postcoital
  - Occasionally overt menorrhagia, metrorrhagia
Diagnosis of Cervicitis

- Signs: specific, but insensitive. Include:
  - easily induced bleeding ("friability")
  - mucopurulent discharge: swab test
  - edematous ectopy
  - discrete lesions (ulcers): can occur anywhere

- Increased PMN ("polys;" >10-30/HPF) on Gram stain of endocervical secretions: may be sensitive for endocervicitis, but not specific; variable in ectocervicitis
STD as a Cause of Cervicitis

- **Endocervicitis** (mucopurulent cervicitis, MPC)
  - Gonorrhea
  - Chlamydia
  - ? *Mycoplasma genitalium* 10-15%?
  - Other/unknown 40-60%
  ~50%

- **Ectocervicitis**: often associated with vaginal infection
  - Trichomoniasis
  - *Candida albicans* (probable but infrequent)
  - Bacterial vaginosis (?)

- **Discrete lesions**
  - Herpes simplex virus (and other ulcerative agents)
  - Syphilis
  - Human papillomavirus
  - Cervical cancer
The Swab Test to Detect Mucopurulent Endocervical Discharge
Neutrophils embedded in cervical mucus
Superficial Cervical Ulcer
Workup of Cervicitis

- Bimanual pelvic examination to rule out PID
- Test for chlamydia and gonorrhea using most sensitive test available
- Careful examination of vaginal fluid, pH
  - Look for BV, trichomoniasis, *Candida*
- Additional diagnostic tests based on clinical judgement (HSV culture, syphilis serology)
- Consideration of STD risk (partner history etc.)
Treatment of Cervicitis

- Treat for gonorrhea and chlamydia, unless either or both has been excluded by specific testing or prior adequate treatment.

- Persistent or recurrent cervicitis:
  - Azithromycin (*M. genitalium*)
  - Metronidazole (trichomoniasis)
Chronic or Persistent Non-GC, non-CT Mucupurulent Cervicitis

- A very common clinical problem, but no useful data exist on prevalence, incidence, or natural history
- Clinical significance unknown
  - One study suggests adverse pregnancy outcomes (Nugent)
- Re-evaluate at least once for gonorrhea and chlamydia
- Treat with azithromycin at least once to cover *C. trachomatis* and *M. genitalium*
- Be sure partner treated (azithromycin or doxycycline)
- Ablative therapy (laser or cryotherapy) is often used and is anecdotally successful; no data
Vaginal Infections

- Trichomoniasis (~10%)
  - *Trichomonas vaginalis* (protozoan)
  - Sexually transmitted
  - Vaginal discharge, odor, elevated pH

- Bacterial vaginosis (~40%)
  - Overgrowth of mostly normal vaginal bacteria; depletion of protective *Lactobacillus*
  - Sexually associated; sexually transmitted in lesbian women
  - Odor, vaginal discharge, elevated pH

- Candida vulvovaginitis (yeast infection, thrush)
  - *Candida albicans, C. glabrata*
  - Intestinal reservoir; not an STD
  - Vulvar itching, irritation; variable discharge; normal pH
Population-based survey in U.S.
Women 14-49 y.o. asked to self-collect vaginal swab
  - 28% reported symptoms
Swabs used to prepare Gram stain for Nugent scoring and trichomonas culture
BV prevalence 27.4% in
  - Higher among non-white women, douching, WSW, higher no. lifetime sex partners, smoking
Trichomoniasis prevalence 3.1% in 1,999 women
  - 13.5% non-Hispanic blacks
  - Only 15% reported symptoms
  - Higher among 30-49 y.o., lower income/education level, higher no. lifetime sex partners, douching

Koumans 2007, Sex Transm Dis
Sutton 2007, Clin Infect Dis

Epidemiology of Vaginitis: NHANES, 2001-2002
A pH-Based Framework for Evaluating Common Causes of Vaginal Infection

Nyirjesy & Sobel, *Curr ID Reports* 2005
Bacterial Vaginosis
The Basics

• The most common vaginal infection
  - Sexually associated disease (SAD)…
  - but sexual transmission per se remains uncertain

• Symptoms
  - Odor
    • Often spontaneously described as fishy
    • May be prominent after sex
  - Vaginal discharge
    • Usually scant
    • White or gray
    • Non-staining
Bacterial Vaginosis
The Basics

- Bacteriology
  - Depletion of $\text{H}_2\text{O}_2$ producing *Lactobacillus* sp.
  - Overgrowth of multiple components of normal flora
    - Anaerobes
    - *Gardnerella vaginalis*
  - Novel, non-cultured “BV associated bacteria” (BVAB)

- Main diagnostic findings
  - pH >4.5
  - Amines, volatilized by alkalinization (KOH/sniff test; semen)
    - Direct effects of anaerobes’ glycosidase activity & metabolism
    - Putrescine, cadaverine
  - Microscopy
    - Clue cells
    - Altered bacterial flora
The Vaginal Milieu in Bacterial Vaginosis

- Profound loss of $\text{H}_2\text{O}_2$-producing \textit{Lactobacilli}
- Overgrowth of "commensal" anaerobes
- Production of sialidase (IgA destruction), glycosidase, volatile amines
- $\uparrow$ IL-1B, IL-10; $\downarrow$ IL-8, SLPI (secretory leukocyte protease inhibitor)

Nugent = 0

Nugent = 10

Cauci 2004; Cherpes 2008
**BV: an STI?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>- Increasing no. sex partners and other epidemiologic markers of STI risk</td>
<td>- Incident BV occurs in sexually experienced but abstinent women</td>
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<tr>
<td>- Concordance within female sex partnerships (shared vaginal secretions?)</td>
<td>- Seemingly random varation in BV symptoms and Nugent scores in untreated women</td>
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<td>- Rare in women with no/little sexual experience</td>
<td>- Prevalence in some populations seems too high</td>
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<tr>
<td>- BVAB detected in male genital tract</td>
<td>- Treatment of male partners has not improved BV-related outcomes</td>
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<td>- Protective effect of condoms</td>
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Diagnosis of BV

- **Clinical findings (Amsel criteria):** $\geq 3$ of the following:
  - Homogeneous discharge, smoothly coating vaginal walls and introitus
  - pH $>4.5$
  - Clue cells ($>20\%$) on saline microscopy
  - Amine odor on addition of KOH (+whiff test)
    - Putrescine, cadaverine
    - BV Blue® test: uncertain clinical utility

- **Gram stain findings (Nugent scale)**
  - Based on number of lactobacilli and other bacterial morphotypes
  - 0-9 scale: 0-3 normal, 4-6 borderline, 7-9 definite BV
  - Primarily research, but clinically useful in trained hands
Bacterial Vaginosis

Wet Prep: Clue Cell

Vaginal Discharge
Complications Associated with BV

- Pelvic inflammatory disease
- Post-hysterectomy infection
- Pregnancy related complications
  - Postpartum endometritis
  - Postabortal endometritis and PID
  - Preterm labor and delivery
  - Premature rupture of membranes
  - Intra-amniotic infection
    - Histological chorioamnionitis
  - Spontaneous abortion in first trimester (IVF)
Nonpregnant Women

- **Recommended**
  - Metronidazole 500 mg PO bid x 7 d
  - Metronidazole gel 0.75% intravag qHS x 5 d
  - Clindamycin cream 2% intravag qHS x 7 d

- **Alternatives**
  - Clindamycin 300 mg PO bid x 7 d
  - Clindamycin ovules 100 g intravag qHS x 3 d
Treatment of Bacterial Vaginosis (CDC)

Pregnant Women
Systemic therapy preferred, especially for women at high risk for preterm delivery:

- Metronidazole 250 mg PO tid x 7 d
- Metronidazole 500 mg bid x 7 d
- Clindamycin 300 mg PO bid x 7 d
Time to BV Recurrence (ITT), Biweekly MTZ Gel vs. Placebo

Sobel
AJOG
2006
Recurrent BV: Management

- More antibiotic is better: higher cumulative doses (longer therapy, 10-14 days) most effective
  - Mechanism unclear: suppression of overall anaerobic overgrowth allowing for recovery of adequate *Lactobacillus* population, or as yet undefined pathogen
  - Emerging data also support better response of initial BV with higher vaginal doses of MTZ (Sanchez 2004)

- Prevent sexual transmission (condoms, no shared toys): Alkaline pH of sperm (7.5) vs. reinfection? (Trabert 2007; Sanchez 2004)

- Repletion of vaginal lactobacilli
  - Capsules containing human *L. crispatus*
  - First attempted product not effective; second under study
  - Over the counter and yogurt strains don’t work
Trichomoniasis: The Basics

- **Etiology:** *Trichomonas vaginalis*
- Sexually transmitted
  ? colonic reservoir
- Mostly asymptomatic
- Male partners generally asymptomatic; sometimes NGU
- Saline mount insensitive (~50-60%)
  Culture ~70%; PCR required to detect >90% of cases
- Male partners generally asymptomatic; sometimes NGU
New Testing Options for Trich

- Rapid antigen test (OSOM; Genzyme)
  - Significantly better than wet mount ($P = 0.004$) (Huppert 2005)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>OSOM</td>
<td>83.3%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Wet prep</td>
<td>71.4%</td>
<td>100%</td>
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- APTIMA TMA Trichomonas Vaginalis Analyte Specific Reagent (ASR; Gen-Probe)
  - Nucleic Acid Amplification Test
  - Utilizes same technology as APTIMA Combo 2 (for CT/GC)
  - May use same specimen type as used with APTIMA Combo 2 (i.e. vaginal swab, endocervical swab, urine)
Trichomoniasis: Vaginal discharge
The Cervix and Trichomoniasis

- Classic: “strawberry cervix”
  - Focal areas of superficial hemorrhage surrounded by paler mucosa
  - May also see more subtle petechiae
  - More common with relatively moderate-severe *Trichomonas* vaginitis
Cervicitis due to *Trichomonas vaginalis*
Trichomoniasis Treatment

Recommended regimen
- Metronidazole 2 g PO x 1
- Tinidazole 2 g po x 1

Alternative regimen
- Metronidazole 500 mg PO BID x 7d
- Routine use for recurrent/persistent cases

- Metronidazole is safe at all stages of pregnancy
- Tinidazole Category C (don’t use)
- Vaginal therapy is ineffective
- Treat sex partner(s)
Vulvovaginal Candidiasis: The Basics

- **Candida albicans** >90% (others <10%, esp. C. glabrata)
  - Normal vaginal flora
  - Colonic reservoir
- Not sexually transmitted, although male partners sometimes get superficial balanitis, especially in uncircumcised
- Diagnosis: Clinical appearance, low pH, no odor, microscopy
Vulvovaginal Candidiasis

- Vulvar component often dominant
- Most cases still caused by *C. albicans* (>90%)
- Women are often misdiagnosed as having VVC when they really have:
  - Genital herpes
  - Lichen planus
  - Recurrent BV
  - Contact dermatitis
  - Atrophic vaginitis
- Uncomplicated VVC defined by all 4:
  - Sporadic
  - Mild-moderate severity
  - Likely to be *Candida albicans*
  - Non-immunocompromised host

Diagnosis of VVC

- Clinical appearance and symptoms
  - Typically prominent irritative symptoms
  - Minimal discharge
- Laboratory
  - pH <4.5
  - Negative amine odor
  - Microscopy (KOH preparation, Gram stain)
  - Isolation of *Candida* species usually not helpful
    - Nonspecific owing to asymptomatic carriage by most women some of the time and some women all of the time
    - *C. albicans* is normal vaginal flora
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<tr>
<th>Vulvovaginal candidiasis, uncomplicated</th>
<th>Intravaginal therapy</th>
<th>Oral therapy</th>
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<tbody>
<tr>
<td>2% Butoconazole cream (Myclex-3)</td>
<td>5 g per day for 3 days††</td>
<td></td>
</tr>
<tr>
<td>2% Sustained-release butoconazole cream (Gynazole)</td>
<td>One 5-g dose</td>
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<tr>
<td>1% Clotrimazole cream (Myclex-7)</td>
<td>5 g for 7–14 days††</td>
<td></td>
</tr>
<tr>
<td>Clotrimazole (Gyne-Lotrimin 3)</td>
<td>Two 100-mg vaginal tablets per day for 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One 100-mg vaginal tablet per day for 7 days</td>
<td></td>
</tr>
<tr>
<td>2% Miconazole cream</td>
<td>5 g per day for 7 days††</td>
<td></td>
</tr>
<tr>
<td>Miconazole (Monistat-7)</td>
<td>One 100-mg vaginal suppository per day for 7 days††</td>
<td></td>
</tr>
<tr>
<td>Miconazole (Monistat-3)</td>
<td>One 200-mg vaginal suppository per day for 3 days††</td>
<td></td>
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<tr>
<td>Miconazole (Monistat-1 vaginal ovule)</td>
<td>One 1200-mg vaginal suppository††</td>
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<tr>
<td>6.5% Tinocazole ointment (Monistat 1-day)</td>
<td>One 5-g dose††</td>
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<tr>
<td>0.4% Terconazole cream (Terazol 7)</td>
<td>5 g per day for 7 days</td>
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<tr>
<td>0.8% Terconazole cream (Terazol 3)</td>
<td>5 g per day for 3 days</td>
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<tr>
<td>Terconazole vaginal</td>
<td>One 80-mg vaginal suppository per day for 3 days</td>
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<tr>
<td>Nystatin vaginal</td>
<td>One 100,000-U vaginal tablet per day for 14 days</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (Diflucan)</td>
<td>One 150-mg dose orally</td>
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<td>Azole</td>
<td>7–14 days</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (Diflucan)</td>
<td>Two 150-mg doses orally 72 hr apart</td>
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Risk Factors for Recurrent VVC

Maintenance Therapy For Recurrent VVC

- Most recurrent yeast vaginitis caused by sensitive yeast, but high persistence of vaginal yeast following therapy anyway (about 50%)

- Goal of antifungal maintenance therapy:
  - Suppress vaginal colonization
  - Allow inflamed epithelium opportunity to heal

- Induction therapy with either
  - Vaginal imidazole daily x 14 days
  - Fluconazole 150 mg days 1 and 4 x 2 weeks

- Maintenance therapy with either
  - Fluconazole 100-150 mg PO weekly
  - Clotrimazole 500 mg intravaginally weekly

- Low-potency topical steroids for severe vulvitis; nystatin cream, sitz baths
Non-albicans Candidiasis

- Primarily *Candida glabrata*
- Most have higher MIC to azoles, but still clinically susceptible
- Clinical failures with *C. glabrata* often require >1 dose treatment
- Azole failure may respond to topical boric acid (600 mg in gelatin capsules daily 14 d), nystatin, or flucytosine
  - Recurrence may be controlled by alternate day then twice weekly boric acid
- No routine indication for susceptibility testing in uncomplicated VVC
Desquamative Interstitial Vaginitis (DIV)

- A presumably uncommon condition characterized by:
  - Chronic purulent vaginal exudate, often yellow-green
  - Occasional vestibulitis, diffuse vaginal erythema focal erosions
  - Elevated pH (>4.5, often ~6), no amine odor, many WBC on saline
  - Presence of Gram+ cocci (often Group B strep) on Gram stain, few lactobacilli, increased parabasal cells
- Typically older (peri or post-menopause) patients with lower STD prevalence
- Treat with 2% clindamycin cream x 14 days OR 10% hydrocortisone cream, 5 g x 14 days (probably longer)

And if there is no STI?

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<tr>
<th>Process</th>
<th>Comments</th>
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<tr>
<td>Persistent disruptions of vaginal flora</td>
<td>Mechanism unclear, but may involve effect of glycosidases produced by bacteria associated with BV. Treatment of BV associated with enhanced resolution of MPC in one small study.</td>
</tr>
<tr>
<td>Persistent infection with an undefined pathogen</td>
<td>No direct research in MPC yet, but use of cultivation-independent molecular techniques is rapidly expanding the spectrum of bacteria associated with BV, including <em>Atopobium vaginae</em>.</td>
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<tr>
<td>Sustained primary host immune response</td>
<td>Genital mucosa affected in many diseases with immune basis, including psoriasis, Behcet’s syndrome. May be augmented further by effect of endogenous or exogenous sex hormones.</td>
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<tr>
<td>Sustained use of commercial products that disrupt or irritate cervicovaginal mucosa</td>
<td>Many over-the-counter products contain surfactants or other potentially irritating substances (betadine, corn starch, topical anesthetics).</td>
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Acute Vulvovaginitis

Linda O. Eckert, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 24-year-old sexually active woman presents with a 3-day history of vaginal pruritus and increased vaginal discharge. One year before presentation, she had the same symptoms, which resolved with use of an over-the-counter antifungal agent. She uses oral contraceptives for birth control. The physical examination reveals vulvar erythema and normal-appearing vaginal discharge. How should she be evaluated and treated?