Management of Recurrent Vaginitis

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Objectives
After hearing this presentation, the participant should:
- Understand vaginal physiology in the asymptomatic patient
- Be aware of recommended treatments for the three most common causes of vaginitis in the acute and recurrent clinical setting
- Be informed of other vaginal disorders that pose management challenges

Disclosure Statement
Neither myself or any member of my family have a financial arrangement related to the content of this activity or any supporters of this program
Scope of the Problem

- Vaginitis most common reason for patient visits to obstetricians and gynecologists in the USA
- Estimated 20 million office visits annually
- One billion dollars in direct costs for yeast infections annually
- Vulvodynia estimated to occur in 15% of gynecologic patients

Accuracy of Patient Self-diagnosis of Vulvovaginal Candidiasis (VVC)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>33.7%</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>18.9%</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>2.1%</td>
</tr>
<tr>
<td>Mixed vaginitis</td>
<td>21.1%</td>
</tr>
<tr>
<td>Normal flora</td>
<td>13.7%</td>
</tr>
<tr>
<td>Other (dermatoses, etc)</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

Ferris, DG et al. Obstet Gynecol, 2002

Accuracy of Physician Diagnosis of Vaginitis via Saline Wet Mounts

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>39.6%</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>75.0%</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>76.5%</td>
</tr>
</tbody>
</table>

Ferris, DG et al. J Family Pract, 1995
**Vaginal pH**

- **Healthy**  
  pH = 3.0 - 4.5  
  [Lactobacillus acidophilus]

- **Gray Zone**  
  pH = 4.5 - 5.0  
  [Lactic acid H₂O₂]

- **“Abnormal”**  
  pH > 5.0

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**Vaginal Squames and Estradiol**

- Mature  
  pH > 5.0
- Intermediate  
  pH = 4.5 - 5.0
- Parabasal  
  pH < 4.5

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**Measure Vaginal pH!**

- **Vaginal pH Test Strips**
- **Testing Vaginal pH**
If vaginal pH is >5.0 the possibilities are:

- bacterial vaginosis
- Trichomonas vaginalis
- menopause on no hormone replacement
- presence of blood in vagina
- breastfeeding on demand
- presence of topical vaginal medications
- recent intercourse with semen in vagina

Vulvovaginal Candidiasis
Vaginal Candidiasis Diagnosis

- C. albicans
- C. krusei
- C. tropicalis
- C. pseudotropicalis
- C. glabrata (formerly Torulopsis glabrata)

Mycelial forms
Budding yeast
Vaginal Candidiasis
Susceptibility to Antimycotics

C. albicans
Sensitive to azoles, Clotrimazole, miconazole and triazoles, terconazole, fluconazole

C. glabrata
C. krusei
C. tropicalis
C. pseudotropicalis
Resistant to azoles
Sensitive to triazoles

Recurrent/Persistent Vaginal Candidiasis – Risk Factors

Yeasts Love Sugar!

- Glycogen rich vaginal environment of healthy pre-menopausal women
- Pregnancy hormonal milieu
- Diabetes, especially poorly controlled, high glycogen environment, altered immune function

Also

- Broad spectrum antibiotics – alter normal vaginal flora
- OCP’s ± +
- Immune compromise – cancer, chemotherapy, HIV ̏
Longitudinal Study of Vaginal Yeast Colonization in Non-pregnant Women

- 248 women 18-25 years of age
- 60% Caucasian, all from Pittsburgh area

- Cultures for yeast at enrollment, 4, 8, and 12 months
- 96% of positive cultures C. albicans

Results:
- 70% colonized at one point or another, most intermittently
- Only 4% colonized at all 4 visits

Independent risk factors for vaginal yeast colonization:
- Marijuana use in past 4 mo. \( P = 0.001 \)
- DMPA use in past 4 mo. \( P = 0.02 \)
- Sexually active past 5 days \( P = 0.001 \)
- Concurrent colonization GBS, lactobacilli \( P < 0.001 \)
- OCP use NS

What is the Utility of Yeast Cultures?

- To identify non C. albicans yeasts i.e. C. glabrata, etc., that don’t respond to conventional therapies
- To prove or disprove yeast colonization in a persistent, symptomatic patient
- Test of cure in a treated patient

Vulvovaginal Candidiasis Therapy

- Uncomplicated
  - Fluconazole (Diflucan) 150mg oral, single dose, provides therapeutic vaginal concentrations for up to 72 hours
  - Intravaginal miconazole, clotrimazole, terconazole, butoconazole (all imidazole antifungals are fungistatic, may be fungicidal at high doses)
  - Pregnancy, topical (vaginal) azoles for 7 days

Note: Drugs that may have clinically important interactions with fluconazole:
- Calcium channel blockers
- Astemazole
- Warfarin
- Cyclosporin A
- Phenytoin
- Tacrolimus
- Theophylline
- Rifampin

Centers for Disease Control and Prevention, STD Treatment Guidelines, 2015
Clinical Pearl
- Patients presenting with longstanding symptoms of pruritus, burning, often taking polypharmacy of meds for presumed yeast
- Need a “wash out” period of at least 4 weeks of no meds
- Then evaluate with exam, culture, and if positive:
  - Fluconazole 200 mg orally every 3 days for 3 doses
  - Evaluate again in 4-6 weeks, exam, re-culture
  - If positive, consider maintenance fluconazole 150 mg weekly, clotrimazole 500 mg vaginally weekly

Candida glabrata
- Second most common yeast causing symptoms in USA
- Seen more commonly in diabetes, immunocompromise
- Filaments or pseudohyphae not seen on KOH or saline preps; small oval or round spheres
- Diagnosis most often made by culture
- Not usually associated with “cottage cheese” discharge

Treatment
- Boric acid vaginal suppositories (600 mg in size 0 gelatin capsule, once or twice vaginally for 15-20 days)
- Re-culture as test of cure, consider maintenance therapy with 600 mg boric acid vaginally 2-3 x weekly
- Additional strategies for persistent C. glabrata
  - 17% flucytosine in vaginal cream
  - 3-4% amphotericin vaginal cream

Vaginal Trichomoniasis
- Trichomonas vaginalis, flagellated protozoa first described in 1836
- 3 million cases reported annually in the USA
- Asymptomatic in 50% of women, 30% eventually develop symptoms
Trichomonas Vaginalis

- Usually copious, foul smelling discharge
- Vaginal/vulvar discomfort, burning, dyspareunia
- Vagina with marked inflammation, many white blood cells, pH >4.5, epithelium often covered with petechial hemorrhages

T. vaginalis - Diagnosis

- Motile Trichomonads on saline wet mount makes diagnosis secure, but
- Wet mount has a sensitivity of 60-80% compared to culture
- More than $10^3/ml$ live protozoa are required for detection via wet mount

Trichomonas Vaginalis - Therapy

- Metronidazole 500 mg orally twice daily for 7 days
  or 2 grams orally, single dose
  or
- Tinidazole 2 grams orally single dose
- 90-95% cure rate if sex partner treated
  75-80% if partner not treated
- Pregnancy – T. vaginalis associated with adverse pregnancy outcomes; PROM, pre-term delivery, low birth weight. CDC recommends 2 gram oral single dose of metronidazole for symptomatic pregnant women regardless of pregnancy stage
- Side effects of metronidazole
  - Metallic or bitter taste
  - Nausea, vomiting
  - Emetic effect with alcohol
  - Rarely, pancreatitis, blood dyscrasias

Hook, E. Sex Trans Dis. 1999
Recurrent/Metronodazole Resistant Trichomonas Occurs in 4%-10% of Cases

- Metronidazole resists reduces metronidazole to a cytotoxic free radical

Other causes of failure of metronidazole:
- Reinfestation by a non-treated partner
- Interference by other drugs
- Gastrointestinal intolerance
- Non compliance

Narcisi, EM and Secor WE, Antimicrob Agents and Chemotherapy, 1996

Trichomonas Vaginalis
Alternative Therapies for Recurrent Cases

- Tinidazole (Tindamax) – 2 grams oral dose
  - Longer half life (12-14 hours) than metronidazole (6-7 hours)
  - Fewer side effects
  - Drug levels in tissue close to levels in serum
- Clotrimazole (Gyne-Lotrimin)
  - Cures in 48-66% of women intravaginal suppositories for 6 nights
- Paromomycin 6.25% cream, must be compounded, one 4 gram application nightly for 2 weeks, mild vaginal burns, cures in 75% of patients with metronidazole intolerance or resistant Trich.

Hager, WD, Sex Trans Dis, 2004

Bacterial Vaginosis

Normal Vaginal Ecosystem

- $10^6$ bacteria/gram of secretion
- Lactobacillus dominant
- pH = 3.5 - 4.5
- Inhibition of anaerobes by lactic acid, hydrogen peroxide

Bacterial Vaginosis

- $10^7 - 10^{11}$ bacteria/gram
- Lactobacilli absent
- Abundant anaerobes
- Bacteroides sp.
- Peptostreptococci
- Mobiluncus
- Gardnerella
- Mycoplasmas
- pH > 4.5

Biswa MK, Clin Obstet Gynecol, 1993
Bacterial Vaginosis (BV)

Asymptomatic in 50% of women
15% of private gynecology patients
10-30% of pregnant women
5-25% of college students

Predisposing Factors
- Douching
- Antibiotics
- Foreign bodies (tampons, diaphragms)
- Exposure to semen
- Menses
- Multiple sexual partners
- Concomitant STD’s, esp. T. vaginalis
- Early coital experience

Bacterial Vaginosis - Not a Benign Condition

Strong association between BV and:
- Premature rupture of membranes
- Preterm labor
- Chorioamnionitis
- Postpartum endomyometritis
- Post-cesarean wound infection
- Pelvic inflammatory disease
- Post hysterectomy vaginal cuff infection

Sweet, RL. Am J Obstet Gynecol, 1993

Bacterial Vaginosis - Diagnosis

Amsel criteria - three of four must be positive
- Vaginal pH >4.5
- Abnormal, malodorous vaginal discharge
- Amine odor on addition of 10% KOH
- Presence of clue cells on saline wet mount

Diagnosis of BV – Clue Cells on Micro
But also, *look between the cells*
- No lactobacilli
- No leukocytes

*Clinically:*
- No redness, inflammation
- Insignificant host immune response

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**Bacterial Vaginosis - Therapy**
- Metronidazole 500 mg orally twice daily x 7 days
- Metronidazole gel 0.75% one full application (5 grams) vaginally once daily x 5 days
  - or
- Clindamycin cream 2%, one full application (5 grams) vaginally at bedtime x 7 days

**Alternative Regimens**
- Tinidazole 2 grams orally once daily x 2 days
  - or
- Tinidazole 1 gram orally once daily x 5 days
  - or
- Clindamycin 300 mg orally twice daily x 7 days

*Note:*
Treatment recommended for all symptomatic pregnant women, either oral or vaginal regimens

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**Persistent/Recurrent BV**
- In 30-40% of women who respond to treatment, BV recurs within 3 months
- No convincing evidence that BV is a sexually transmitted disease.
  Treatment of male partners has not improved cure rates or reduced recurrences
- Alternate therapies (acidic douches, lactic acid gels, probiotics) have generally been ineffective

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Fredricsson, B et al. Gynecol Obstet Invest, 1989
Holley, RL, Schwebke JR, Sex Trans Dis, 2004
Biofilms as a Cause of Recurrent BV

- Certain strains of Gardnerella vaginalis form biofilms, a dense web of bacterial cells encased in a fibrillar exopolysaccharide network
- These biofilms increase bacterial resistance to host immune defenses, pH extremes and antimicrobial agents
- This appears to be the prime mechanism for the relative resistance to metronidazole and high recurrence rate in patients prone to bacterial vaginosis


Recurrent Bacterial Vaginosis

Recommended Maintenance Regimens

- Initial 10 day course of metronidazole gel 0.75% followed by met gel twice weekly for 4 months
  Results: Infection recurred in 26% of met gel vs 59% of placebo patients (P=.001)
- Metronidazole or tinidazole 500 mg twice daily for 7 days followed by 21 days of 600 mg boric acid vaginally, followed by twice weekly met gel for 16 weeks
  Results: cumulative cure at 12, 16, and 28 weeks from initial visit was 87, 78, and 65%, respectively with failure rate of 50% by 36 week follow-up
  Reichman, O et al., Sex Trans Dis, 2009

Non-Vaginitis Vaginitis

- Clinical scenario
  Healthy pre-menopausal woman with longstanding vaginal itching, non-malodorous discharge, usually polypharmacy
  Exam: excellent vaginal estrogen effect, no inflammation, saline wet mount● healthy vaginal squames, no vaginitsis organisms, no WBC reaction, negative yeast culture
  Diagnosis: Excess physiologic vaginal secretions
  Treatment: Reassurance
- Another scenario –
  Same patient, same exam, totally negative wet mount, cultures
  Treatment: Patient will not accept “normal” convinced that something is wrong, wants medication
  Assessment:
  - Somatization due to stress, unhappiness
  - Neurosis
  - Avoidance of sexual intimacy with partner
  - Patient usually poorly accepts need for counseling, anxiolytics, antidepressants
**Vulvodynia**

**Vaginodynia**

*Recommend* –
Amitriptyline (Elavil) 10 mg at bedtime, increase by 10 mg weekly, maximum 40 mg until return visit; common side effect drowsiness.

or

Gabapentin (Neurontin) 100 mg tid, may increase to 300 mg tid; common side effects drowsiness, ataxia.

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**Final Thoughts**

- STUDY vaginal saline wet mounts
- Don’t be afraid to tell patients they are normal (if they really are normal)
- Diflucan won’t cure everything that itches

*The End*

*Thank You*