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)

Vulvovaginal candidiasis	33.7%
Bacterial vaginosis	18.9%
Trichomoniasis	2.1%
Mixed vaginitis	21.1%
Normal flora	13.7%
Other (dermatoses, etc)	10.5%

Ferris, DG et al. Obstet Gynecol, 2002

Accuracy of Physician Diagnosis of Vaginitis via Saline Wet Mounts

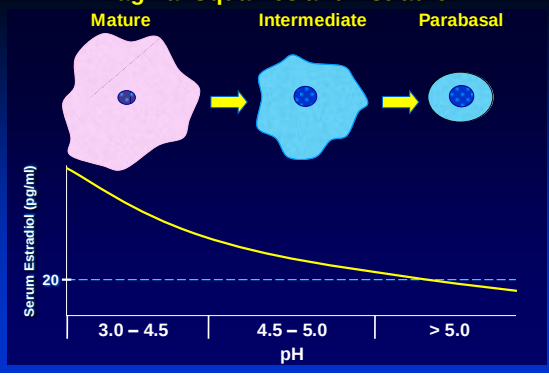
Vulvovaginal candidiasis	39.6%
Trichomoniasis	75.0%
Bacterial vaginosis	76.5%

Ferris, DG et al. J Family Prac, 1995

Vaginal pH

- Healthy pH = 3.0 - 4.5
  - Gray Zone pH = 4.5 - 5.0
    - "Abnormal" pH >5.0
- Lactobacillus acidophilus
  - Lactic acid H_2O_2

Vaginal Squames and Estradiol



Measure 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. kruseii
  - C. tropicalis
  - C. pseudotropicalis
  - → Mycelial forms
- C. glabrata (formerly Torulopsis glabrata)
  - → Budding yeast

Vaginal Candidiasis Susceptibility to Antimycotics

- **C. albicans** — Sensitive to azoles, Clotrimazole, miconazole and triazoles, terconazole, fluconazole
- **C. glabrata, C. kruseii, 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
- 98% 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=.001
• DMPA use in post 4 mo.	P=.02
• Sexually active past 5 days	P=.001
• Concurrent colonization GBS, lactobacilli	P<.001
• OCP use	NS

Beigi, RH et al, Obstet Gynecol, 2004

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

Vulvovaginal Candidiasis Therapy

- Complicated/Recurrent/Persistent

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

Nyirjesy, P, Obstet Gynecol, 2014
CDC STD Guidelines, 2015

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 presistent C. glabrata
  - 17% flucytosine in vaginal cream
  - 3-4% amphotericin vaginal cream

Nyirjesy, P, Obstet Gynecol, 2014

Vaginal Trichomoniasis

Trichomonas vaginalis, flagellated protozoa first described in 1836

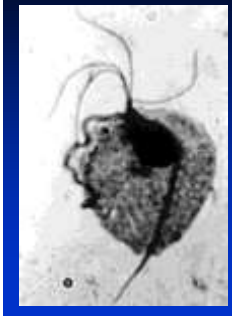
3 million cases reported annually in the USA

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

Hook, E. Sex Trans Dis, 1999
Ryu, JS et al. Yonsei Med J, 1999

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

Centers for Disease Control and Prevention, STD Treatment Guidelines, 2015

Recurrent/Metronodazole Resistant Trichomonas Occurs in 4%-10% of Cases

Metronodazole passively infuses into organism →

← Ferrodoxin in organism reduces metronidazole to a cytotoxic free radical

- Metronidazole resistant organisms have reduced levels of intracellular ferrodoxin
- Clinically resistant trichomoniasis often treated with increased dosage of metronidazole for longer periods (oral doses > 3 g/day associated with high risk of serious side-effects)

Other causes of failure of metronidazole:
- Reinfection 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
Nyirjesy, P et al, Clin Infec Dis, 1998

Bacterial Vaginosis

Normal Vaginal Ecosystem	*Bacterial Vaginosis*
10^{5-6} bacteria/gram of secretion	10^{9} - 10^{11} bacteria/gram
Lactobacillus dominant	Lactobacilli absent
pH = 3.5 - 4.5	Abundant anaerobes
Inhibition of anaerobes by lactic acid, hydrogen peroxide	Bacteroides sp.
	Prevotella
	Peptostreptococci
	Mobiluncus
	Gardnerella
	Mycoplasmas
	pH >4.5

Biswas 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
Soper, DE et al. Am J Obstet Gynecol, 1990

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

Amsel, R et al. Am J Med, 1983

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

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

Centers for Disease Control and Prevention, STD Treatment Guidelines, 2015

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

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

Patterson, JL et al, Am J Obstet Gynecol, 2007
Swidsinki, A et al, Am J Obstet Gynecol, 2008

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)
  Sobel, JD et al, Am J Obstet Gynecol, 2006
- 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 vaginitis 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.

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