An Integrative Approach to Recurrent Vaginitis

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Objectives

• Define integrative medicine.
• Briefly describe the normal vaginal ecosystem.
• Provide an overview of the diagnosis of recurrent bacterial vaginosis and vaginal candidiasis.
• Discuss conventional and integrative approaches for the treatment of vaginitis and the evidence for their use.
Case Study

- Tanisha is a 25 year old African American woman who suffers from recurrent vaginal infections.
- She says “I feel like I have an infection every month. Sometimes it’s BV and sometimes it’s yeast”. She is embarrassed by the vaginal odor and the amount of vaginal discharge. In addition, she experiences vaginal irritation and itching.
- She is hoping there is some kind of treatment that will stop this cycle of vaginal infections from recurring. She is particularly interested in using something other than antibiotics; she doesn’t like taking them so often. She would like to use something more “natural”.

Integrative Medicine

- The practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing.” Consortium of Academic Health Centers for Integrative Medicine
- Combines mainstream medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness. NCCAM
CAM Treatments for Chronic Vaginitis

Women referred for evaluation of chronic vaginal symptoms completed a survey (N= 481)
• 65% used CAM (42% in 1997)
  • 47% yogurt and 35% acidophilus
  • 14% other health food supplements
  • 13% low carbohydrate diet
  • 8.5% garlic
• Increased perceived stress
• Symptoms interfered with life

Nyirjesy et al. (2011, 1997) Obstetrics and Gynecology

Psychosocial Issues

• Women with recurrent VVC (Irving, 1998) had:
  • More depression, less satisfaction with life, poorer self esteem, increased perceived life stress and it seriously interfered with sexual and emotional relationships
• Women with recurrent BV (Payne, 2010)
  • Frustrated and distressed by vaginal odor and discharge
    • Impedes social, personal and work relationships
    • Leads to hypervigilant routines of hygiene
• Women were distressed by the diagnosis of vaginitis (Karasz, 2003)
  • There were many misperceptions about the cause: infidelity, cancer, past sexual behavior
  • Rated symptoms moderate to severe
Vaginal Ecosystem

Vaginal Health: Role of *Lactobacilli*

- Pathogens and lactobacilli migrate naturally from rectum
- Dominant in vagina *L. crispatus* and *L. jensenii*
- Produce lactic acid that maintains a normal vaginal pH of 4.0 (3.8-4.2).
- Produce hydrogen peroxide that is toxic to the anaerobic microflora.
- Their micropili (tiny projections from the cell wall) adhere to receptors on the vaginal epithelial cells preventing adherence of potential pathogens.
Vaginal Candidiasis Diagnosis

- Vaginal itching with thick white “curdy or cottage cheese” discharge adherent to vaginal walls
- May have vulvitis, fissures or rash
- pH normal <4.5
- Wet mount:
  - Saline: few WBCs, rare clue cells, many lactobacilli
  - KOH: hyphae (sensitivity 50% CDC), no amine smell

Treatment of Acute VVC

OTC or prescription intravaginal regimens:
- Butoconazole, clotrimazole, miconazole, nystatin, tioconazole, terconazole, etc.

Oral regimen:
- Fluconazole 150 mg in a single dose
- Oral and vaginal equally effective
- Treatments >80-90% effective
- Vaginal creams are oil-based and should not be used with condoms or diaphragms

CDC, 2010
Recurrent VVC

- Definition: >4 episodes in a year (<5% of women)
- Obtain vaginal culture to confirm diagnosis and identify unusual species (Hoffstetter, 2008)
  - If non-albicans VVC use longer duration of therapy or use non-azole regimen
- 94% of women (n=427) with recurrent VVC had * albicans species (Sobel, 2004)
- Most women with recurrent VVC are sensitive to antifungal but have persistent infection (50%)
- Goal of therapy is to suppress colonization

Why is there Recurrence?

- Inadequate treatment
- Non-albicans species
- Reduction of protective flora due to use of antibiotics
- Immunodeficiency
  - DM hyperglycemia enhances *C. albicans* adherence to vaginal mucosa
  - Systemic candida in HIV
  - Subnormal T lymphocyte response to candida
- Contraceptive use: oral contraceptives
- Resistance to azoles 7.5%
- Mechanical factors: heat, increased moisture e.g. tight pants

(lavazzo, 2011)
Treatment of Recurrent VVC: Azoles

- Initial regimen of 7-14 days topical therapy or fluconazole 150 mg every 3 days x3 (Sobel, 2004)
- Then “azole” treatment x 6mos such as fluconazole 150mg po once weekly for 6 mos.
  - 91% cured at 6 mos vs. 36% placebo
  - 43% cured at 12mos vs. 22% placebo
  - Monitor liver enzymes if indicated.

Boric Acid and VVC

Review of 14 studies including 2 RCTs, boric acid was compared to many different azoles (Iavazzo, 2011)

- Mycologic cure rate 40-100% compared to 50-100% with azoles
- Recurrence rate 0-46%, not statistically significant
- Well tolerated
  - Adverse events: Vaginal burning <10%, watery discharge, vaginal erythema
  - Little systemic absorption from vagina
- In patients with *C. glabrata* cure rates were 64% (Sobel, 2003).
Use of Boric acid

- Boric acid is both bacteriostatic and fungistatic (DeSeta, 2009)
- Boric acid traditionally used as an antiseptic, insecticide, etc.
- Dose: Boric acid 600mg in a gelatin capsule is inserted in the vagina daily for 2 weeks.
- You can also get pharmaceutical grade boric acid and fill your own capsules (0 size).
- Maintenance dose of twice weekly to prevent recurrences
- It is available without a prescription and is inexpensive.
- Precaution: Should not be used during or right before pregnancy. Keep away from children.

Other Ideas

- Use a progestin only method such as DMPA to reduce estrogenic environment of vagina (Dinnerstein, 1986; Toppozada, 1979)
- Consider restricting the amount of sugar and dairy in diet.
Bacterial Vaginosis

- Prevalence is 15% to 30% (non-pregnant women in USA)
- Normal *Lactobacilli* in the vagina are replaced with high concentrations of anaerobic bacteria
- Cause of microbial alteration is not fully understood
- Up to 50% of women with BV may not report any symptoms.
- BV is a risk factor for:
  - STIs (HIV acquisition) and other genital infections
  - Urinary tract infections
  - Adverse pregnancy outcomes
  - Pelvic inflammatory disease

Risk Factors for Acquisition of BV

Sexual risk factors
- early sexual debut
- a new sexual partner
- multiple sexual partners
- high number of lifetime sexual partners
- frequent vaginal sex
- a female sexual partner
- receptive anal sex before vaginal intercourse
- sex with an uncircumcised male partner
- douching
- race/ethnicity

Demographic risk factors
- low social economic status
- poor hygiene
- marital status
- black race

Microbiological risk factors
- lack of vaginal H2O2-producing lactobacilli
- STIs most commonly trichomoniasis
- HIV infection
- herpes simplex virus type 2 infection

Other risk factors
- pregnancy
- cigarette smoking
BV Associated Bacteria

- Actinobacteria
  - *Gardnerella vaginalis*
  - *Mobiluncus curtsii* and *M. mulleris*
  - *Atopobium vaginae*
  - *Eggerthela* ssp.
- Bacteroidetes
  - *Prevotella* spp.
- Fusobacteria
  - *Leptotrichia* ssp.
  - *Sneathia* spp.
- Fermicutes (Clostridia)
  - *Megasphaera* spp.
  - *Peptostreptococcus* spp.
  - *Fusobacterium* spp.
  - BV-associated bacteria 1 (BVAB 1)
  - BVAB 2
  - BVAB 3
- Mycoplasmas
  - *Mycoplasma hominis*
  - *Ureaplasma urealyticum*

Bacterial Vaginosis Diagnosis

- Amsell criteria (3 out of 4)
  - pH≥4.7
  - Positive amine/whiff test
  - Clue cells
  - Homogeneous grey discharge
- Gold standard in research Nugent’s criteria
- Point of care tests such as BVBlue have good sensitivity and specificity
CLINICAL PEARL

pH testing very helpful in making an accurate diagnosis

Acute BV Treatment

- Metronidazole 500 mg twice daily for 7 days
- Metronidazole gel 0.75%, 5 g intravaginally once daily for 5 days
- Clindamycin cream 2%, 5g intravaginally at bedtime for 7 days

CDC, 2010
Treatment of Recurrent BV

- Treat for longer period of time - 2 weeks
- Change to a different antibiotic
- Prophylactic maintenance therapy for 4-6 months
  - Vaginal metronidazole twice weekly
  - Oral metronidazole 3 times a week
- Variable cure rates with antibiotics
  - 70-80% at 30 days
  - 60% at 6 months
  - 48% at 12 months
- Increasing prevalence of multi-drug resistant pathogens

Triple Therapy with Boric Acid

Hypothesis: vaginal biofilm adherent to epithelial cells in BV facilitates persistence of bacterial pathogens - boric acid removes this biofilm

- Retrospective chart review (Reichman, 2009)
  - 7 days with nitroimidazole
  - 21 days of vaginal boric acid 600 mg daily
  - If remission then metronidazole gel twice weekly for 16 weeks
- Cure rates (Amsel criteria)
  - 88% (60 episodes) at 12 weeks just nitroimidazole and boric acid
  - 65% (57 episodes) at 28 weeks triple therapy
  - 50% at 36 weeks
Why use Probiotics?

- Old thinking: they work by producing antimicrobial substances like H2O2, adhere to epithelial cells and have in vitro inhibitory activity against BV pathogens.
- New thinking: adhesiveness not as important, more important to survive pH, cope with hormonal changes and modulate host responses, outcompete organisms already present.
- Mechanisms involved in homeostasis: production of antimicrobials and surface-altering biosurfactants, immune modulation and displacement of pathogens. (MacPhee, 2010)
- Disruption of BV biofilms demonstrated with \textit{L. rhamnosus} GR-1 (McMillan, 2011)

Normal Vaginal Flora

Consists mainly of lactobacillus species:
- \textit{L. crispatus} (main \textit{H}_2\textit{O}_2 producing species)
- \textit{L. jensenii}
- \textit{L. gasseri}
- \textit{L. inus}
- \textit{L. vaginalis}
- \textit{L. rhamnosus}
- \textit{L. fermentum}

Phase 2a Lactin-V study at UCSF (Cohen, Hemmerling, Korn, et al.): \textit{L. crispatus} colonized, safe and acceptable
Probiotics Cochrane Review (2009)

Two Studies found probiotics to be beneficial:

• DB PCT (n=125) oral metronidazole 7 days with oral probiotics *L. rhamnousus GR* and *L. reuteri RC14* 30 days (Anukam 2006)

• RPCT (n=32) parallel group design probiotic *L. acidophilus* with estriol 0.03 mg vaginal tablets pregnant and non-pregnant women (Parent 1996)

• Recurrence not reported
• Good tolerability and safety profiles
• Not sufficient evidence for or against recommending probiotics

Use of Lactobacillus

• Look for products that contain lactobacillus found in vagina
  • OTC probiotic (Femdophilus): 5 billion *L. rhamnosus GR-1* and *L. reuteri RC-14*, take 1-2 daily

• Supplement should have at least one billion organisms per capsule. Take one capsule twice a day between meals for 7-14 days.

• Quality issues: see brands tested by ConsumerLabs.com
• Eat yogurt daily, live culture, European probably better. Don’t use in vagina.
Issues in BV research

- 7-33% of healthy women lack appreciable number of *Lactobacillus* species in the vagina
- They are replaced by other lactic acid producing bacteria
- Health maintained as long as production of lactic acid continues
- Women with BV have different microbial profiles, there is a lot of biodiversity among women
- Current study of the vaginal microbiome may shed some light
  - using molecular based techniques to understand vaginal flora

(Lamont, 2011)

Tea Tree Oil (*Melaleuca alternifolia*)

- There is a long history of traditional use by herbalists as a topical antibiotic and anti-fungal.
- The terpenes are probably the active ingredient.
- Inhibit both anaerobic and aerobic bacteria in *in vitro* studies (Hammer 1999, Cox, 2000).
- Inhibited *C. albicans in vivo* -mice (Mondello, 2006)
- One case study of BV cured when tea tree oil added to vaginal pessary (Blackwell, 1991).
- Effective against candidal species *C. albicans* (D'Auria, 2001), *C. glabrata* and *C. parapsilosis* (Hammer, 1998).
Use of Tea Tree Oil

- Tea tree oil (crushed leaves) in gelatin capsule
- Often found in preparations combined with other herbs
- Dosage: 200mg suppository used once or twice daily for 6 days.
- Some people may be sensitive to herb (contact dermatitis)
- The cost for one treatment regimen is about $24.
- Do not use during pregnancy

Evidence for Botanicals

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<tr>
<th>Botanical</th>
<th>In Vitro C. Albicans</th>
<th>In Vitro Non- Albicans Species</th>
<th>In Vitro Other Varinilis</th>
<th>Clinical studies</th>
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<tr>
<td>Propolis</td>
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<td>For BV: (Blackwell, 1991; Imhaf, 2005)</td>
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<td>Garlic (Allium sativum)</td>
<td>(Santana, 1995)</td>
<td>(Moore, 1977)</td>
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<td>Berberine (Berberis aristata)</td>
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<td>Bergamot (Citrus bergamia)</td>
<td>(Soffar, 2001)</td>
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<td>Clove oil (Eugenia aromatica)</td>
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<td>Lavender oil (Lavandula augustifolia)</td>
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<td>In vivo mice (Maruyama, 2008)</td>
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<td>Mentha suaveolens EO</td>
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<td>In vitro/In vivo mice (Pietrella, 2011)</td>
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Recommendations for Tanisha

She has had recurrent mixed vaginal infections; both VVC and BV and prefers not to take antibiotics.

• For both antibacterial and antifungal activity:
  • Use boric acid suppositories once daily for 2 weeks or
  • Tea tree oil suppositories
• Then a 3-6 month course of probiotics to re-colonize the vagina with lactobacilli and prevent BV.
• Discuss the risk factors for recurrent vaginal infections including sexual practices
• Discuss hormonal contraception that may be beneficial to her vaginal ecosystem.

Patient education

• If you have a history of recurrent VVC, request an anti-fungal treatment with prescriptions for antibiotics.
• Abstain from vaginal or oral sex during treatment.
• Condoms can break when used with vaginal creams.
• Using condoms for one month after treatment may reduce the risk of recurrence.
• Come in for an exam when you are symptomatic.
• If you have had recurrent infections, bring your medical records from other providers.
• Do not douche.
• Discuss your questions, concerns and feelings about vaginitis with your provider.
Summary

- Although conventional treatments have excellent efficacy for acute vaginitis, relapse rates are high.
- While many alternative treatments have been used traditionally to treat vaginitis and do show some efficacy in vitro, more clinical research is needed to support their use.
- Most alternative treatments pose little safety risk thus are good options especially for the prevention of recurrent vaginitis.