Vulvar Skin Conditions and Vaginitis Cases

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Learning Objectives

- Describe the differential diagnosis for vaginal discharge and the clinical signs and symptoms associated with each of the major causes
- Outline the tests needed to confirm diagnosis and appropriate treatments.
- Explain the challenges of recurrent and resistant infections

Disclosures

- Bayer: litigation consultant
- Sebela Pharmaceuticals:
  - Investigator proctor in phase III trial of a copper IUD (VeraCept)
- For this lecture, I have no relevant financial relationships with any commercial interests to disclose

International Society for the Study of Vulvar Disease (ISSVD)

- 2015: Vulvar Intraepithelial Neoplasia (VIN)
- 2011: Terminology and Classification of Vulvar Dermatological Disorders
- 2006: Classification of Vulvar Dermatoses
- 2003: Terminology and Classification of Vulvodynia
2011 ISSVD Terminology and Classification of Vulvar Dermatological Disorders: An Approach to Clinical Diagnosis

- Step 1: Define the lesion by choosing one or more nouns
  - Blister, nodule, macule, papule, plaque, rash, etc.
- Step 2: Choose appropriate adjectives to modify the noun
  - Color, surface, margination, configuration
- Step 3: Formulate a list of differential dx from 8 groups
- Step 4: Reduce the number to 2-3 possibilities
- Step 5: Confirm the diagnosis

### Lesion Example

#### Skin colored lesions
- Papules and nodules
- Plaques

#### Red lesions: patches, plaques
- Eczematous and lichenified
- Red patches and plaques

#### Red lesions: papules, nodules
- Papules
- Nodules

#### White lesions
- Papules and nodules
- Patches and plaques

#### Dark colored lesions
- Patches
- Papules and nodules

#### Blisters
- Vesicles, bullae
- Pustules

#### Erosions and ulcers
- Erosions
- Ulcers

#### Edema
- Skin colored
- Pink or red edema

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### Case 1: Joslyn 33 year old G₁ P₁

- c/o “itchy bumps” on her vulva for the past year
- Has not responded to OTC medications
- States that her partner does not have similar lesions
- Exam: multiple 1-2 mm flesh colored papules asymmetrically distributed on the labia majora
- Has similar symmetrical lesions below her eyes
Case 1: Joslyn

- What additional information would you want in
  - History of the present complaint?
  - Medication history?
  - Sexual history?
  - Family history?
- Do you think that she needs a biopsy?
- What is your initial differential diagnosis?

Poll: Which Diagnosis Is Most Likely?

1. Molluscum contagiosum
2. Genital warts
3. HSIL of vulva (VIN)
4. Skin tags
5. Syringoma
6. I have no idea

Skin-colored Papules and Nodules

1. Papillomatosis of the vestibule
2. Molluscum contagiosum
3. Genital warts (HPV infection)
4. HSIL of vulva (VIN)
5. Skin tag (acrochordon, fibroepithelial polyp)
6. Mucinous cysts of the vestibule and medial labia minora
7. Epidermal cyst (syn. epidermoid cyst; epithelial cyst)
8. Mammary-like gland tumor (hidradenoma papilliferum)
9. Syringoma
10. Basal cell carcinoma
Micropapillomatosis

A single base for each projection

HPV typically has multiple projections coming off a single base

Molluscum Contagiosum

- Due to pox virus (Molluscum contagiosum virus)
- Inner thighs, mons, labia minora
- Can be solitary; usually 5-30 lesions
- Circular, firm, smooth; 2-6 mm diameter
  - Umbilicated center in 20%
  - May appear as vesicles
- Usually white or skin colored
  - Pink or red: spontaneous resolution likely

Molluscum Contagiosum

- Spread by skin-to-skin contact: sex, sports

- Treatment
  - Wait for resolution
  - Self-treatment with toothpick
  - Cryotherapy
  - Office curettage (on vulva, edge of 30g needle)
  - Imiquimod (off-label)
  - Podophylox (off-label)
“Juvenile” EGW

Good Imiquimod candidate!

Vestibular Cysts

Epidermoid Cyst
Epidermoid Cysts

- Usually multiple, but can be single
- Contain sebaceous material; liquid or dried
- Usually have yellow or cream color
- May have “BB shot” or “dried bean” texture
- No treatment, unless infected

Syringoma

- Adenoma of eccrine sweat glands
- Onset in adolescence or later
- Multiple skin-colored to yellowish pruritic papules
  - 1-5 mm diameter
  - Located on the labia majora
  - Asymmetrically distributed
- When large numbers, may coalesce to form bumpy plaque
- Lower eyelids, axillae, neck, chest, upper arms, and abdomen

Syringoma: Treatment

- Observation
- Electrodesiccation
- Laser
- Cryotherapy
- Excision (if few lesions)

Fox Fordyce Disease

- Blockage of apocrine sweat duct
  - Mainly axilla, vulva, nipples
- Intense itching, triggered by emotional stimuli
- Multiple, small, firm, dome-shaped papules
  - Skin colored to slightly yellow
- Treatments
  - Topical steroids or pimecrolimus
  - Topical clindamycin
  - Topical tretinoin 0.025% cream
  - Oral contraceptives
  - Surgical options: electrocautery, surgical excision of the affected skin
Case 1: Take Home Points

- Not all skin colored vulvar papules are due to STIs (e.g., genital warts) or other infectious agents
- Unless the diagnosis is obvious (genital warts, molluscum, epidermoid cysts, etc), a typical lesion should be biopsied before treatment
- For many conditions in the differential diagnosis, treatment is more hazardous than observation (e.g., edipermoid cysts)

Case 2: Maria 48 Year old

- c/o itchy “rash” on her vulva for the last 6 months
- At times the itching is so severe that she is unable to make it through a full day of work
- Her PCP advised her to try OTC 0.5% hydrocortisone cream, but it anything, the itching got worse
- She has Type 2 diabetes on metformin
- A bilateral vulvar rash is noted
Case 2: Maria

- What additional information would you want in
  - History of the present complaint
  - Medication history
  - Sexual history
  - Family history
- Which office tests would you do, if any?
- Do you think that she needs a biopsy?

Poll: Which Diagnosis Is Most Likely?

1. Vulvar candidiasis
2. Tinea cruris vulvitis
3. Irritant contact dermatitis
4. Psoriasis
5. I don’t know

Red Patches and Plaques

2A. Eczematous and lichenified diseases
   1. Allergic contact dermatitis
   2. Irritant contact dermatitis
   3. Lichen simplex chronicus
   4. Lichenification superimposed on an underlying preceding pruritic disease

Red Patches and Plaques

2B. No epithelial disruption
   1. Candidiasis
   2. Psoriasis
   3. HSIL of vulva (VIN)
   4. Lichen planus
   5. Plasma cell (Zoon) vulvitis
   6. Extramammary Paget disease
Vulvar Candidiasis

- **Symptoms**
  - Vulva will be very itchy

- **Presentation**
  - Erythema + satellite lesions
  - Often excoriated
  - Occasionally: thrush, LSC thickening if chronic

- **Diagnosis**
  - Skin scraping KOH
  - *Candida* culture or PCR

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Vulvar Candidiasis

- **Treatment**
  - Topical antifungal therapy daily for 7-14 days, or fluconazole 150 mg PO repeat in 3 days
  - *Plus*: TAC 0.1% or 0.5% ointment QD-BID

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Tinea Cruris: “Jock Itch”

- **Asymmetric lesions on proximal inner thighs**
  - Plaque rarely involves scrotum; not penile shaft
  - Well demarcated red plaques with accentuation of scale peripherally; no satellite lesions

- **Treatment**
  - Mild: topical azoles BID x10-14d, terbinafine
  - Severe: fluconazole 150 mg QW for 2-4 weeks
  - If inflammatory, add TAC 0.1% on 1st 3 days
Psoriasis: Treatment

- **Consult with dermatologist if not previously diagnosed**
- **Decrease mitotic rate**
  - Tar (LCD 5% in TAC 0.1% ointment)
  - Topical retinoids (Tazarac®, Avage®)
  - Anthralin (Dritho-Scalp)
- **Decrease inflammation**
  - Topical steroid ointment (e.g., TAC)
  - Vitamin D analogues (calcipotriene; Dovonex®)
  - Clobetasol-Dovonex combination
  - Tar preparations, topical steroids
  - Calcineurin inhibitors (tacrolimus, pimecrolimus)
Immunomodulators (Biologics)

- FDA approved for moderate to severe psoriasis and failed to respond to traditional therapy or who have psoriatic arthritis
- Options
  - Etanercept (Enbrel®)
  - Infliximab (Remicade®)
  - Adalimumab (Humira®)
  - Ustekinumab (Stelara®)
  - Golimumab (Simponi®)
  - Apremilast (Otezla®)...only oral option
  - Secukinumab (Cosentyx®)
  - Ixekizumab (Taltz®)

Contact Dermatitis

- Irritant contact dermatitis (ICD)
  - Elicited in most people with a high enough dose
  - Rapid onset vulvar itching (hours-days)
- Allergic contact dermatitis (ACD)
  - Delayed hypersensitivity
  - 10-14d after 1st exposure; 1-7d after later exposures
- Atopy, ICD, ACD can present with
  - Itching, burning, swelling, redness
  - Small vesicles or bullae more likely with ACD

Contact Dermatitis

- Common contact irritants
  - Urine, feces, excessive sweating
  - Saliva (receptive oral sex)
  - Repetitive scratching, overwashing
  - Detergents, fabric softeners
  - Topical corticosteroids
  - Toilet paper dyes and perfumes
  - Hygiene pads (and liners), sprays, douches
  - Lubricants, including condoms
Contact Dermatitis

- **Common contact allergens**
  - Poison oak, poison ivy
  - Topical antibiotics, esp neomycin, bacitracin
  - Spermicides
  - Latex (condoms, diaphragms)
  - Vehicles of topical meds: propylene glycol
  - Lidocaine, benzocaine
  - Fragrances

Contact Dermatitis: Treatment

- Exclude contact with possible irritants
- Restore skin barrier with sitz baths, compresses
- After hydration, apply a bland emollient
  - White petrolatum, mineral oil, olive oil
- Short term mild-moderate potency steroids
  - TAC 0.1% BID x10-14 days (or clobetasol 0.05%)
  - Fluconazole 150 mg PO weekly
- Cold packs: gel packs, peas in a “zip-lock” bag
- Doxypin or hydroxyzine (10-75 mg PO) at 6 pm
- If recurrent, refer for patch testing
**Case 2: Take Home Points**

- Duration of symptoms is a helpful tip-off
- Examine other skin surfaces for similar lesions
- Office microscopy helps to rule-in candidiasis
- Unless the diagnosis is obvious (candidiasis, *Tinea cruris* vulvitis, contact dermatitis), a typical lesion should be biopsied before treatment
- Don’t use combination steroid- antifungal drugs

**Case 3: Sulema 51 year old**

- Recently immigrated from Guatemala
- c/o right vulvar itching and irritation for 6 months
- Referred from a community clinic for a raised white vulvar lesion on right labia minora
- She not had noticed, nor had she been told about, the white lesion in the past

**Case 3: Sulema**

- What additional information would you want in
  - History of the present complaint
  - Medication history
  - Sexual history
  - Family history
- Does she need a biopsy?
- What is your initial differential diagnosis?
**Poll: Which Diagnosis Is Most Likely?**

1. Lichen sclerosus  
2. Lichen simplex chronicus  
3. HSIL of the vulva  
4. Squamous cell carcinoma of the vulva  
5. A combination of some of the above conditions  
6. I don’t know

**4B: White Patches and Plaques**

1. Vitiligo  
2. Postinflammatory hypopigmentation  
3. Lichen sclerosus  
4. Lichen simplex chronicus  
5. Lichen planus  
6. HSIL of the vulva (VIN)  
7. Squamous cell carcinoma

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**Post-inflammatoty hypopigmentation (Leukoderma)**

- Lack of pigmentation in scarred area from trauma or ulceration  
- Most commonly seen after herpetic and syphylotic ulcers  
- No family history, as with albinism or vitiligo  
- No biopsy or treatment necessary

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**Lichen Sclerosus: Natural History**

- Most common vulvar dermatosis  
- Prevalence: 1.7% in a general GYN practice  
- Cause: autoimmune condition  
- Bimodal age distribution: older women and children, but may be present at any age  
- Chronic, progressive, lifelong condition
Lichen Sclerosus: Natural History

- Most common in Caucasian women
- Can affect non-vulvar areas
- Part (or all) of lesion can progress to VIN, differentiated
- Predisposition to vulvar squamous cell carcinoma
  - 1-5% lifetime risk (vs. < 0.01% without LS)
  - LS in 30-40% women with squamous vulvar cancers

Lichen Sclerosus: Findings

- **Symptoms**
  - Most commonly, itching
  - Often irritation, burning, dyspareunia, tearing
  - 58% of newly-diagnosed patients are asymptomatic
- **Signs**
  - Thin white “parchment paper” epithelium
  - Fissures, ulcers, bruises, or submucosal hemorrhage
  - Vulvar architecture: loss of labia minora, fusion of labia, phimosis of clitoral hood
  - Depigmentation (white) or hyperpigmentation
  - Introital stenosis

“Early” Lichen Sclerosus

- Hyperpigmentation due to scarring
- Loss of labia minora

Lichen Sclerosus: Loss of Labia Minora

Photo courtesy of Dr Hope Heafner
Lichen Sclerosus: “Figure of Eight” or “Hour Glass” Appearance

Photo courtesy of Dr. Hope Heafner

Lichen Sclerosus: Treatment

• Biopsy mandatory for diagnosis
• Preferred treatment
  – Clobetasol (or halobetasol) 0.05% ointment QD x4 wks, then QOD x4 wks, then twice-weekly for 4 wks
  – Taper to med potency steroid (or clobetasol) 2-4 times per month for life
  – Explain “titration” regimen to patient, including management of flares and recurrent symptoms
  – 30 gm tube of ultrapotent steroid lasts 3-6 mo
  – Monitor every 3 months twice, then annually

Lichen Simplex Chronicus = Squamous Cell Hyperplasia

• Cause: an irritant initiates a “scratch-itch” cycle
• LSC classified as
  – Primary (idiopathic)
  – Secondary (superimposed upon lichen sclerosus, candida vulvitis; vulvar contact dermatitis)
• Presentation: always itching; burning, pain, tenderness
• Thickened leathery red (white if moisture) raised lesion
• In absence of atypia, no malignant potential
  – If atypia present, classified as VIN

Lichen Simplex Chronicus
**L. Simplex Chronicus: Treatment**

- **Removal of irritants or allergens**
- **Treatment**
  - Triamcinolone acetonide (TAC) 0.1% ointment BID x 4-6 weeks, then QD
  - Other moderate strength steroid ointments
  - Intralional TAC once every 3-6 months
- **Anti-pruritics**
  - Hydroxyzine (Atarax) 25-75 mg QHS
  - Doxepin 25-75 mg PO QHS
  - Doxepin (Zonalon) 5% cream; start QD, work up

**Vulvar Intraepithelial Neoplasia (VIN): Prior to 2004**

- Grading of VIN-1 through VIN-3, based upon degree of epithelial involvement
- *The mnemonic of the 4 P’s*
  - Papule formation: raised lesion (erosion also possible, but much less common)
  - Pruritic: itching is prominent
  - “Patriotic”: red, white, or blue (hyperpigmented)
  - Parakeratosis on microscopy

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**ISSVD Classification of VIN 2004**

- Since VIN 1 is not a cancer precursor, abandon use of term
  - Instead, use “condyloma” or “flat wart”
- Combine VIN-2 and VIN-3 into single “VIN” diagnosis
- Two distinct variants of VIN

<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyloma</td>
</tr>
<tr>
<td>VIN 2</td>
<td>VIN-usual (VIN-u)</td>
</tr>
<tr>
<td>VIN 3</td>
<td>VIN-usual (VIN-u)</td>
</tr>
<tr>
<td>Differentiated</td>
<td>VIN-differentiated (VIN-d)</td>
</tr>
</tbody>
</table>

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**ISSVD Classification of VIN 2015**

<table>
<thead>
<tr>
<th>ISSVD 1986</th>
<th>ISSVD 2004</th>
<th>ISSVD 2015</th>
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</thead>
<tbody>
<tr>
<td>VIN 1</td>
<td>Flat condyloma, HPV effect</td>
<td>LSIL of the vulva</td>
</tr>
<tr>
<td>VIN 2-3</td>
<td>VIN-usual (VIN-u)</td>
<td>HSIL of the vulva</td>
</tr>
<tr>
<td>Differentiated</td>
<td>VIN-differentiated (VIN-d)</td>
<td>DVIN</td>
</tr>
</tbody>
</table>

*Journal of Lower Genital Tract Disease 2016; 20 (1):11-14*
**HSIL of the Vulva (VIN)**

- Usually HPV-related (mainly type 16)
- More common in younger women (30s-40s)
- Often asymptomatic
- Lesions elevated with rough surface; flat lesions can be seen
- Often multifocal (periurethral, perianal)
- Multicentric in 50% (concurrent CIN, VaIN or AIN)
- Strongly associated with immunocompromise, smoking
- Low malignant potential (5-20%)
  - Precursor to 20% of vulvar cancer

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**Vulvar HSIL**

**White Warty type**

**Vulvar HSIL**

*Note the raised, whitened, irregular surface*

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**Vulvar HSIL**

**Basaloid type**

*Photo courtesy of Dr M Sideri*
Vulvar HSIL: warty-basaloid type

FIGURE 3. Vulvar intraepithelial neoplasia, usual type, with white-gray color changes and irregular borders.

Image courtesy of Natalie A. Saunders, MD.

Vulvar HSIL: Hyperpigmented Lesions

Hypermelinated Vulvar HSIL
Vulvar HSIL: Gray-Brown

Photo courtesy of C Dunton, MD

Anal Intraepithelial Neoplasia

Photo courtesy of Dr Hope Heafner

DVIN: Differentiated Type VIN

- Usually in older women with LS, LSC, or LP
- Not HPV related
- Far less common than VIN-usual type
- Symptoms: long history of pruritus and burning
- Findings
  - Red, pink, or white papule; rough or eroded surfaces
  - A persistent, non-healing ulcer
  - Unifocal, unicentric
- More likely to progress to SCC of vulva than VIN-u
  - Precursor to 80% of vulvar cancer

DVIN (Differentiated VIN)

Photo courtesy of Dr M Preti
HSIL of the Vulva

- **Risk of invasion:** greater if immunocompromised (steroids, HIV), >40 years old, previous lower genital tract neoplasia
- **Treatment**
  - Wide local excision: highest cure rate, esp. hair-bearing
  - CO₂ laser ablation: best cosmetic result
  - Topical agents: imiquimod
  - Skinning or simple vulvectomy rarely used
- **Recurrence** is common (48% at 15 years)
  - Monitor @ 6,12 months, then annually
- **Prevention:** HPV-2, HPV-4, or HPV-9 vaccine

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Treatment of VIN with Imiquimod

- **Treatment with 5% imiquimod BIW x16-20 weeks**
- **Off-label use of this drug**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>IMQ response</th>
<th>Control response</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>vanSeters 2008</td>
<td>52</td>
<td>81%</td>
<td>0%</td>
<td>Progression to cancer in 6% patients over 12 months</td>
</tr>
<tr>
<td>Mathiesen 2007</td>
<td>21</td>
<td>81%</td>
<td>10%</td>
<td>67% ↓ dosing 2° to adverse effects</td>
</tr>
<tr>
<td>Le 2007</td>
<td>33</td>
<td>77%</td>
<td>No controls</td>
<td>Recurrence @16 months - IMQ: 21% - Surgery: 53%</td>
</tr>
<tr>
<td>Rosen 2007</td>
<td>49</td>
<td>86%</td>
<td>No controls</td>
<td></td>
</tr>
</tbody>
</table>
**Case 3: Take Home Points**

- Unless the diagnosis is obvious (lichen sclerosus in a postmenopausal woman), a representative area of the lesion should be biopsied before treatment.
- Any suspicion of HSIL of the vulva (VIN) requires biopsy.
- Lesions suspicious for melanoma must be diagnosed with excisional biopsy rather than punch biopsy.

**DDX: Chronic Vulvovaginal Symptoms**

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections (70%)</td>
<td>Vaginal trichomoniasis (VT)</td>
</tr>
<tr>
<td></td>
<td>Bacterial vaginosis (BV)</td>
</tr>
<tr>
<td>Skin Conditions</td>
<td>Vulvovaginal candidiasis (VVC)</td>
</tr>
<tr>
<td></td>
<td>Vulvar dermatoses (LS, LP, LSC)</td>
</tr>
<tr>
<td></td>
<td>Vulvar intraepithelial neoplasia (VIN)</td>
</tr>
<tr>
<td></td>
<td>Desquamative Inflammatory vaginitis (DIV)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Vestibulodynia</td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Physiologic, psychogenic</td>
</tr>
</tbody>
</table>

**200 Patients in a 3rd Care Vaginitis Clinic**

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact dermatitis</td>
<td>21%</td>
</tr>
<tr>
<td>Recurrent vulvovaginal candidiasis</td>
<td>21%</td>
</tr>
<tr>
<td>Atrophic vaginitis</td>
<td>15%</td>
</tr>
<tr>
<td>Local provoked vestibulodynia</td>
<td>13%</td>
</tr>
<tr>
<td>Physiologic discharge</td>
<td>9%</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>7%</td>
</tr>
<tr>
<td>Other causes</td>
<td>14%</td>
</tr>
</tbody>
</table>

Nyirjesy P, Obstet Gynecol 2006;108:1185-91

**The Vaginal Environment**

- A dynamic ecosystem...10^9 bacterial colony-forming units
- Normal discharge is clear-white, odorless, high viscosity
- Normal bacterial flora is dominated by lactobacilli
  - *Mainly Lactobacillus crispatus and L. jensenii*
  - *Not L. acidophilis or bulgaricus*
- Lactic acid maintains a normal vaginal pH of 3.8 to 4.7
- Acidic environment and other host immune factors inhibits the overgrowth of bacteria
- Some lactobacilli produce H_2O_2, a potent microbicide
History: Vulvovaginal Complaints

- Take nothing for granted, especially “yeast infections”
- Your job is to make an accurate diagnosis…it’s the cornerstone of effective treatment
- Ask about
  - Discharge, itching, burning, irritation, pain, odor
  - Acute vs. chronic symptoms
  - Episodic exacerbations vs. constant
  - Worse with contact (e.g., intercourse)
  - Treatments: what, when, did anything help?

Nyirjesy P. Management of Persistent Vaginitis. OG 2014;124:1135-46

Exam: Vulvovaginal Complaints

- Vulva
  - Inflammation
  - Red, white or brown lesions
  - Fissures, ulcers, loss of labia minora
- Vestibule
  - Swab test (pain mapping)
- Vagina
  - Discharge, inflammation, erosions, synchiae, papules
- Cervix: mucopus, contact bleeding, leukoplakia
- Mouth, eyes, axillae, elbows and knees, as indicated

Lab: Vulvovaginal Complaints

- Vaginal pH
- Swab of discharge in saline to make
  - 10% potassium hydroxide (KOH)suspension
  - Saline (NaCl) suspension
- Whiff test (aka amine test)
- Ancillary tests
  - GC/Ct, based on risk factors or if WBC on microscopy
  - Candidal culture or PCR
  - Trich PCR
  - No indication for “bacterial culture and sensitivity”

My “Trick Infection” Won’t Go Away!!

- 25 year old woman with complaint of vaginal discharge, itching, and irritation
- Exam: frothy greenish discharge, trich on saline
- Treated with Metronidazole 2 grams x1 dose
- Returned 2 weeks later with same symptoms; exam again showed motile trichomonads
- Re-treated with metronidazole 2 grams PO
- Returned 6 weeks later with same symptoms; exam again showed motile trichomonads
CDC 2015: Trichomoniasis Screening and Testing

- **Screening indications**
  - HIV positive women: annually
  - Consider if “at risk”: new/multiple sex partners, history of STI, inconsistent condom use, sex work, IDU

- **Newer assays**
  - OSOM Rapid Trich®: ↑ sensitivity, specificity vs. slide
  - Aptima TMA® (NAAT)

- **Retest** 3 months after treatment

VT: Office Laboratory Tests

- **NaCl slide**: motile trichomonads, many WBC
  - Trichomonads sensitive to light, heat, air, saline concentration
  - Evaluate slide quickly with fresh normal saline

- **KOH slide**: unremarkable

- **pH**: 6.0 - 7.5

- **Amine test**: mildly positive

NaCl Suspension: Trichomoniasis

Saline: 40X objective

Source: Seattle STD/HIV Prevention Training Center at UW

Trichomoniasis: Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptima TMA</td>
<td>+4 (98%)</td>
<td>+3 (98%)</td>
<td>$$$$</td>
<td>NAAT (like GC/Ct)</td>
</tr>
<tr>
<td>Culture</td>
<td>+3 (83%)</td>
<td>+4 (100%)</td>
<td>$$$$</td>
<td>Not in most labs</td>
</tr>
<tr>
<td>Point of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Affirm VP III</td>
<td>+3</td>
<td>+4</td>
<td>$$$$</td>
<td>DNA probe</td>
</tr>
<tr>
<td>• OSOM Rapid</td>
<td>+3 (90%)</td>
<td>+4 (100%)</td>
<td>$$</td>
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</tr>
<tr>
<td>NaCl suspension</td>
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<td>+4 (100%)</td>
<td>$c</td>
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<tr>
<td>Pap smear</td>
<td>+2</td>
<td>+3</td>
<td>n/a</td>
<td>Confirm if low prevalence</td>
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</tbody>
</table>

Accuracy data: Huppert CID 2007
Trichomoniasis Treatment

- **Recommended regimen**
  - Metronidazole 2 g PO x 1 dose
  - Tinidazole 2 g PO x 1 dose
- **Alternative regimen**
- **Women with HIV infection**
  - Metronidazole 500 mg PO BID x 7d
- **Pregnancy**
  - Metronidazole 2 g PO x 1 dose (all trimesters)
  - Tinidazole is a Category C drug in pregnancy
- Treat sex partner(s)

Trichomoniasis: Treatment Failure

- Most recurrent cases result from having sex with an untreated partner
- **First failure**, re-treat with
  - Metronidazole 500 mg PO BID x 7 days
- **Repeat failure**, treat with
  - Tinidazole 2 g PO x 5 days, or
  - Metronidazole 2 g PO x 5 days
- *Susceptibility testing: call the CDC: 404-718-4141*

Trich Tips: Advice to Clinicians

- May have been transmitted by *any* lifetime partner
- Evaluate NaCl suspensions *pronto* (< 5 minutes)
- Use *fresh* NaCl solutions (< 1 month old)
- Question “dead Trich” on microscopy
- Single dose MTZ *still* is the treatment of choice
- Tinidazole worth the investment if prior failure or adverse effects (but not urticaria or anaphylaxis)
- Pregnant women can be treated with metronidazole

I Keep Getting BV!!

- 35 year old woman states that she develops vaginal discharge and malodor “every 2 or 3 months”
- Diagnosed with BV 18 months ago; since then, has been treated four times, each with a different topical drug
- Each treatment improved malodor “for a while”
- Has started douching to manage malodor
- This is “ruining her life”…too embarrassed to enter into a new relationship
**BV: Pathophysiology**

- **Non-inflammatory** bacterial overgrowth
  - 100 x increase *Gardnerella vaginalis*
  - 1000 x increase in anaerobes
  - More pathogen types (*Mobiluncus, Mycoplasmas*)
- Suppression of H₂O₂-producing *Lactobacillus crispatus* and *L. jensenii* (*L acidophilus* is not present)
- >50% women carry *G. vaginalis* in the absence of BV
- Bacterial “C/S” of vaginal fluid doesn’t help in the diagnosis of BV....or of any other vaginal infection

**Model of BV Pathogenesis**

- Decreased *Lactobacillus* → Increased Anaerobes
- *suppression by amines*

**Microbial Shifts With BV**

- BV is characterized by 100- to 1000-fold increases in pathogenic bacteria
- Lactobacilli concentrations decrease substantially

**Model of BV Pathogenesis**

- Antibiotics → Decreased *Lactobacillus* → Increased Anaerobes
- Douching → Decreased *Lactobacillus* → Increased Anaerobes
- Viral phage → Increased pH
- Adhesion to Sperm → BVAB
  - *Atopobium vaginae*
**BV: Sexually Associated or Transmitted?**

- "Sexually associated" in heterosexuals
  - Rare in virginal women
  - Greater risk of BV with multiple male partners
  - Condom use decreases risk

  *But*
  - No BV carrier state identified in men
  - Treatment of partner does not affect recurrences

- Women having sex with women (WSW)
  - Infected vaginal fluid between women causes BV
  - Concurrence in lesbian couples suggests horizontal TM

**BV: Clinical Presentation**

- About 50% of women with BV are asymptomatic
  - 75% no malodor, 58% no abnormal discharge

- Symptoms
  - Profuse watery discharge
  - Aminous malodor, especially after intercourse
  - Few or no irritative symptoms

- Signs
  - Homogeneous discharge: white or slate gray
  - Bubbly texture possible, but < trichomonas
  - Usually no vulvar or vaginal inflammation

**BV: Clinical Diagnosis**

- Amsel Criteria: 3 or more of
  - Homogenous white discharge
  - Amine odor ("whiff" test)
  - pH ≥ 4.7 (most sensitive)
  - Clue cells > 20% (most specific)

- Spiegel criteria, Nugent score: Gram stain with
  - Few or no gram positive *Lactobacillus* spp.
  - Excess of other gram negative morphotypes

**Characteristic Discharge With BV**
NaCl Suspension: Bacterial Vaginosis

Saline: 40X objective

Source: Seattle STD/HIV Prevention Training Center at UW

Clue Cells on Saline Suspension

>20% of epithelial cells are clues

Reduced Lactobacilli

Ragged cell border

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensit</th>
<th>Specif</th>
<th>Cost</th>
<th>Comment</th>
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<tbody>
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<td>Labor intensive</td>
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<td>Point of care tests</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>* Affirm VP III</td>
<td>+4</td>
<td>+3</td>
<td>$$$</td>
<td>DNA probe</td>
</tr>
<tr>
<td>* OSOM BV Blue</td>
<td>+3</td>
<td>+3</td>
<td>$§</td>
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<tr>
<td>* G vag PIP</td>
<td>+2</td>
<td>+3</td>
<td>$$$</td>
<td>CLIA moderate</td>
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<td>+2</td>
<td>$</td>
<td>CLIA waived</td>
</tr>
<tr>
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<td>+2</td>
<td>c¢</td>
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<tr>
<td>Pap smear</td>
<td>+1</td>
<td>+2-3</td>
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<td>Coccobacilli</td>
</tr>
</tbody>
</table>
### CDC 2015: BV Treatment

#### Recommended regimens
- Metronidazole 500 mg PO BID x 7 days
- Metronidazole gel 0.75% 5g per vagina QD x 5 days
- Clindamycin 2% cream 5g per vagina QHS x 7 days

#### Alternative regimens
- Tinidazole 2 g PO QD for 2 days
- Tinidazole 1 g PO QD for 5 days
- Clindamycin 300 mg PO BID x 7 days
- Clindamycin ovules 100 mg per vagina QHS x 3 days

### Recurrent BV

- Recurrent disease remains common
  - 25% in 4-6 weeks, up to 80% within a year
- Reasons for recurrence unclear
  - Persistence of vaginal biofilm
  - Failure of Lactobacilli to recolonize
  - Persistence of unidentified host factor
  - Inadequate length of therapy
  - Reinfection

### CDC 2015: Recurrent BV

- Suppression with metronidazole vaginal gel twice weekly for 4-6 months (after full initial treatment)
- Metronidazole 500 mg PO BID x 7 days
  - then intravaginal boric acid 600 mg daily x 21 days
  - then MTZ gel twice weekly for 4-6 months
- Metronidazole 2g + fluconazole 150 mg once monthly

### Treatment Of Recurrent BV

- Defined > 3 episodes per year
- Study design
  - MTZ gel 0.75% BID x 10 d, then 2x/ wk
  - MTZ gel 0.75% BID x 10 d, then placebo
  - Both groups treated x 3 months, then
  - Followed for 6 months
- Results
  - 83% remain symptom free on treatment
  - 33% remain symptom free on placebo
  
  Sobel JD et al. *Int J Gynecol & Obstet* 1999
Recurrent BV

• No evidence yet to support use of probiotics
• Don’t douche…with anything!
• Use of condoms by male partners
• Clean sex toys (or use condoms) between uses
• Avoid vaginal insertion after anal insertion of a finger or penis

Bacterial Vaginosis Tips

• Diagnosis
  – “Clue cell positive” if >20% of epithelials are clues
  – Amine test with residue on speculum, not slide
  – Vaginal pH between 4.5-6.0
  – “Homogenized milk” vaginal discharge
  – Culture and Pap smear have no role in diagnosis
• Treatment is a trade-off of convenience and cost
  – Oral MTZ: lots of side effects, but cheap
  – Topicals: fewer side effects, but more expensive

“Will I Ever Get Rid of This Yeast?”

• Ms L is a 44 year old woman with recurrent vulvovaginal itching x 4 years
• No history of diabetes or corticosteroid use
• Treated with multiple course of topical antifungal drugs, with temporary relief
• Occasional vaginal discharge; no malodor
• Wants to “get rid of the yeast” once and for all!

Recurrent Vulvovaginal Itching

• Chronic or recurrent vaginal candidiasis
  – Candida albicans
  – Candida glabrata
• Chronic or recurrent vaginal trichomoniasis
• Recurrent genital herpes
• Contact dermatits (irritant or allergic)
• Vulvar dermatoses
  – LS, LSC, lichen planus, psoriasis
• VIN (vulvar intraepithelial neoplasia)
**Evaluation: Recurrent VV Itching**

- Symptom diary
- Meds: topical E (post-menopause), antibiotics, steroids
- Detailed search for anatomic causes (e.g., fistula)
- Saline, KOH slides during symptomatic period
- Vaginal pH, amine test
- Candidal culture (and speciation), or PCR
- If at risk for glucose intolerance, screen for diabetes
- If vaginitis is chronic, severe, recalcitrant, or if oral thrush or lymphadenopathy, consider HIV

**VVC: Laboratory**

- **KOH suspension**
  - C. albicans: pseudohyphae and blastospores (buds)
  - C. glabrata: blastospores only
- **NaCl suspension**: many WBC, normal lactobacillus
- **pH**: 4-6
- **Amine test**: negative
- **Confirmatory tests**
  - Point of care test: Affirm VP III
  - Candida culture (not: fungus culture)
  - Candida PCR

---

**Candida Pseudohyphae**

- **10% KOH: 10X objective**
  - Lysed squamous epithelial cell
  - Masses of yeast pseudohyphae

**Source**: Seattle STD/HIV Prevention Training Center at UW

**Candida Pseudohyphae**

- **Saline: 40X objective**
  - Yeast pseudohyphae
  - Yeast buds
  - PMNs
  - Squamous epithelial cells

**Source**: Seattle STD/HIV Prevention Training Center at UW
**Candida Blastospores (Buds)**

Saline: 40X objective

Source: Seattle STD/HIV Prevention Training Center at UW

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**CDC 2015: VVC Classification**

- **Uncomplicated VVC (80-90%)**
  - Sporadic or infrequent VVC, and
  - Mild-to-moderate VVC, and
  - Likely to be Candida albicans, and
  - Immune competent

- **Complicated VVC (10-20%)**
  - Recurrent VVC (> 4x per year), or
  - Severe VVC, or
  - Non-albicans candidiasis, or
  - Uncontrolled DM, immunosuppression, pregnancy

---

**Treatments for VVC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>OTC</th>
<th>Prescription</th>
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</thead>
<tbody>
<tr>
<td>Anti-fungal drug</td>
<td>7 d</td>
<td>3 d 1 d 7 d 3 d 1 d</td>
</tr>
<tr>
<td>Butoconazole</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>X X</td>
<td>X</td>
</tr>
<tr>
<td>Miconazole</td>
<td>X X X</td>
<td></td>
</tr>
<tr>
<td>Terconazole</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>Tioconazole</td>
<td>X X</td>
<td></td>
</tr>
<tr>
<td>Fluconazole (PO)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

**Uncomplicated VVC Treatments**

- **Non-pregnant women**
  - 3 and 7 day topicals have equal efficacy and price
  - Offer *either* 1 or 3 day topical or oral fluconazole
    - **Topical**: quickly soothing, but inconvenient
    - **Oral**: convenient, but effect is not immediate

- **If first treatment course fails**
  - Re-confirm diagnosis *(r/o dual infection)*
  - Treat with an alternate antifungal drug
  - Perform Candida *culture* to confirm and speciate
Complicated VVC Treatment

Severe VVC
- Advanced findings: erythema, excoriation, fissures
- Topical azole therapy for 7-14 days, or

Compromised host
- Topical azole treatment for 7-14 days
- Fluconazole 150 mg PO; repeat Q3 days 1-2 times

Pregnancy
- Topical azoles for 7 days

Candida glabrata Vaginitis
- Intense vulvovaginal burning, rather than itching
- More likely in diabetics, immunocompromised
- 54% of women have no resolution of sx after treatment
- KOH: Candida spores (buds), not hyphae
- Treatments
  - Imidazoles for 7-14 days
  - Terconazole x7-14 days may cover better
  - Boric acid 600 mg in gelatin capsule PV daily x 14 days
  - Topical gentian violet
  - Fluconazole not recommended (by CDC)

Non-albicans Candida Vulvovaginitis
> 50% C. glabrata are resistant to azoles
  - Boric acid 600mg pv qHS x 14d
  - Fluconazole 400mg daily for 7d + topical azole
  - Compounded Amphotericin B 4%/flucytosine 17% vaginal cream, 70grams, 4 grams nightly for 14 days

Complicated VVC Treatment

Recurrent VVC (RVVC)
- > 4 episodes of symptomatic VVC per year
- Most women have no predisposing condition
  - Partners rarely source of infection
- Confirm with Candidal culture before maintenance therapy; also check for non-albicans species
- Early self-treatment: 3 days cream @ symptom onset

Sobel Lancet 2007
**Complicated VVC Treatment**

- **Recurrent VVC: Treatment**
  - Treat for 7-14 days of topical therapy or fluconazole 150 mg PO q 72h x 3 doses, then
  - Maintenance therapy x 6 months
    - Fluconazole 150 mg PO 1-2 per week
    - Itraconazole 100 mg/wk or 400 mg/month
    - Clotrimazole 500 mg suppos 1 per week
    - Boric acid 600 mg suppos QD x14, then BIW
    - Gentian violet: Q week x2, Q month X 3-6 mo

**Treatment of Candida in Pregnancy**

- 1.4 million pregnancies in Denmark
- Linked administrative databases
- Each fluconazole-exposed case matched with 4 controls
- SAB between 7-23 weeks

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**“They Can’t Find the Reason for My Vaginal Discharge!”**

- Betty 40 year old G2 P1 Vietnamese American with severe vulvovaginal irritation, burning, and copious watery yellow discharge
- Not sexually active for 10 years
- Multiple courses of OTC topical antifungal drugs and topical vulvar 1% cortisone with no relief

**Physical Exam**

- Generalized vulvar erythema
- Significant vaginal erythema
- Copious watery yellow/brown discharge without malodor
Microscopy of Vaginal Fluid

- pH: >4.5
- NaCl suspension: 4+ WBC, no lactobacillus, many parabasal cells
- Amine test: negative
- KOH suspension
  - No hyphae
  - No buds

Desquamative Inflammatory Vaginitis (DIV)

- Noninfectious inflammatory vaginitis in a setting of normal or low estrogen
- Characterized by
  - Chronic purulent vaginal exudate; yellow-green
  - Diffuse vaginal erythema
  - An increase in WBC and parabasal cells
  - Absent lactobacilli
  - Elevated vaginal pH (>4.5, often ~6)

Differential Diagnosis
DIV vs. Lichen Planus

- Lichen planus
  - Exhibits erosions as well as redness
  - Affects the mouth and the vulva
  - Produces remarkable scarring
- DIV does NOT
  - Erode
  - Affect any other skin surfaces
  - Scar
**DIV: Treatment**

- 2% clindamycin vaginal cream (anti-inflammatory)
- Intravaginal corticosteroids (hydrocortisone)
  - 25mg Anusol HC rectal supp nightly (or 1/2 supp BID)
- If recalcitrant, use both in combination
- When symptoms abate
  → decrease frequency or discontinue
  → restart again prn for discomfort
- Some Rx weekly fluconazole to prevent candidiasis
- Estrogen vaginal cream if GSM

Edwards L, Goldbaum BE. OBG Management, 2014;26:30-37

**Tools Of The Trade**

**Management of Persistent Vaginitis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>pH</th>
<th>Microscopy</th>
<th>Amines</th>
<th>Gold Std</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;4.7</td>
<td>Unremarkable + WBC</td>
<td>Neg</td>
<td>Clinical dx</td>
</tr>
<tr>
<td>VVC</td>
<td>&lt;4.7</td>
<td>Hyphae, blastospores</td>
<td>Neg</td>
<td>Culture, PCR</td>
</tr>
<tr>
<td>BV</td>
<td>&gt;4.7</td>
<td>Clue cells, coccobacilli</td>
<td>Pos</td>
<td>Gram stain</td>
</tr>
<tr>
<td>VT</td>
<td>Varies</td>
<td>Motile trichomonads</td>
<td>Variable</td>
<td>T Vag PCR</td>
</tr>
<tr>
<td>Atrophic</td>
<td>&gt;4.7</td>
<td>Parabasal cells, decreased mixed flora</td>
<td>Neg</td>
<td>Maturation index</td>
</tr>
<tr>
<td>DIV</td>
<td>&gt;4.7</td>
<td>Parabasal cells, increased WBC, decreased mixed flora</td>
<td>Neg</td>
<td>Clinical diagnosis</td>
</tr>
</tbody>
</table>


**Management of Persistent Vaginitis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>None indicated</td>
</tr>
<tr>
<td>Candida VV</td>
<td>Fluconazole 150 mg Q3 days x3, then Q wk x6 months</td>
</tr>
<tr>
<td>Non-albicans Candida</td>
<td>Boric acid 600 mg capsules QD x 2 weeks</td>
</tr>
<tr>
<td>BV</td>
<td>MTZ 0.75% gel 5 g/day x10d, then twice weekly</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>Tinidazole 2 gm daily for 5 days</td>
</tr>
<tr>
<td>DIV</td>
<td>Clindamycin 2% cream QD x 4 weeks</td>
</tr>
<tr>
<td>GSM</td>
<td>Estradiol cream daily for 1-2 weeks, then bi-weekly, Estradiol ring x 90 days or tablet (0.01 mg) bi-weekly</td>
</tr>
</tbody>
</table>

References: Vulvar Dermatology


References: Vulvar Dermatology


References: Vulvar Dermatology


References: Vaginitis

- Diseases Characterized by Vaginal Discharge in CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR Recomm Rep 2015;64 (No. RR-3): 1-137
References: Trichomoniasis

• Thorley N, Ross J. Intravaginal boric acid: is it an alternative therapeutic option for vaginal trichomoniasis? Sex Transm Infect. 2018; 94(8):574-577
• Gaydos CA, Klausner JD. Rapid and point-of-care tests for the diagnosis of Trichomonas vaginalis in women and men. Sex Transm Infect. 2017; 93(S4): S31-S35

References: Candida Vaginitis


References: Bacterial Vaginosis

• Donders G. Diagnosis and management of BV and other types of abnormal vaginal bacterial flora: a review. Obstet Gynecol Surv. 2010;65(7):462-73

Additional References

• Mason MJ, Winter AJ. How to diagnose and treat aerobic and desquamative inflammatory vaginitis. Sex Transm Infect. 2017; 93(1):8-10