Infectious Diseases and Women’s Health

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• Women’s health is affected by a variety of genital tract and non-genital tract infections
  • Viral, bacterial, and parasitic infections
  • Some are transmitted sexually
  • Some are associated with significant consequences, including malignancy
  • Some have an altered course during pregnancy or affect the developing fetus

Objectives of today’s talk—Discuss:
• Common vulvovaginal infections encountered in primary care practices
  • Bacterial vaginosis, Trichomonas, Monilia (yeast), Herpes simplex
  • Human papillomavirus
  • Scope of disease, vaccine
• Current infection of interest
  • Zika virus

Case #1
• 44 year old perimenopausal woman presented for colposcopy for low-grade squamous epithelial lesion (LSIL) on Pap smear.
• Reported a 2 week history of significant vulvovaginal burning and itching; had called PCP’s office and Rx for estrogen cream was given.
• On exam had erythematous, edematous vulva with vesicles and ulcerations
• Herpes simplex virus (HSV) PCR was sent and returned positive.
• Saline wet mount showed evidence of trichomonads and clue cells
• Colposcopy was deferred due to discomfort, this was subsequently undertaken

Herpes simplex virus (HSV)
• Primary HSV
Herpes Simplex Virus (HSV)

- Genital infection caused by HSV-2 in 70-90% of cases and HSV-1 in 10-30%
- Transmitted by sexual contact and from mother to fetus prenatally or at time of delivery
- In women, lesions may involve vulva, perineum, buttocks, vagina, cervix
- Primary infections often associated with fever, malaise, anorexia, inguinal adenopathy
  - Inguinal adenopathy may occur
- 80% of patients have recurrences, with varying frequency
  - Recurrences are more frequent with HSV-2 than HSV-1

HSV—Symptoms and Signs

- Symptoms:
  - Asymptomatic (77%, 90%)
  - Pain, pruritus, tingling, dysuria, tenesmus, vaginal discharge
- Signs:
  - Tender vesicles which ulcerate and may have exudate
  - Inguinal adenopathy with primary infection
HSV – 2 and “The tip of the iceberg”

Iceberg represents all those with HSV-2 antibody

HSV -- Transmission

- Transmission can occur during prodrome, when lesions are present, or during asymptomatic viral shedding.

- Asymptomatic viral shedding:
  - Occurs more frequently during early months after initial infection.
  - Has been shown to occur on approximately 2-3% of days.

Diagnosis of HSV—CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137

- Tissue culture
- Sensitivity decreases as ulcerative lesions heal.
- PCR
- More sensitive than tissue culture.
- More important for treatment of infections affecting the CNS and encephalitis.
- **Failure to detect HSV with culture or PCR does not indicate absence of HSV, as viral shedding is intermittent.**
- Direct immunofluorescence (IF)
- Less sensitive than culture and PCR.
- Serologic tests for HSV-1 and HSV-2
- May help to confirm diagnosis of “false-negative” culture, and to outline contacts.
- Cytology (Tzanck preparation or Pap smear)
- Less sensitive or specific and should not be used as initial test.

Treatment of genital HSV

- Primary or first episode:
  - Acyclovir 200 mg orally TID for 7–10 days, or
  - Acyclovir 500 mg orally 5 times a day for 7–10 days, or
  - Valacyclovir 1 g orally twice a day for 7–10 days, or
  - Famciclovir 350 mg orally TID for 7–10 days.
  - **With any of above regimens, extended treatment is recommended if healing is incomplete after 10 days of treatment.**

- Severe first episode:
  - Acyclovir 10 mg/kg IV every 8 hours for 2–7 days or until clinical improvement, followed by oral therapy to complete 10 days course.
  - Famciclovir 150 mg orally TID for 21 days.

CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137
Treatment of genital HSV, con’t

- **Episodic therapy for recurrent HSV**
  - Acyclovir 400 mg orally TID or 800 mg orally twice a day for 5 days, or
  - Acyclovir 800 mg orally TID for 2 days, or
  - Valacyclovir 1 gram orally twice a day for 5 days, or
  - Famciclovir 500 mg orally once, then 250 mg twice a day for 2 days

- **Suppressive Therapy for HSV**
  - Reduces frequency of recurrences by 70 – 80%
  - Decreases the rate of HSV-2 transmission to discordant heterosexual partners

- **Regimens include:**
  - Acyclovir 400 mg orally twice a day, or
  - Valacyclovir 500 mg orally once a day, or
  - Famciclovir 1 gram orally once a day, or
  - Famciclovir 250 mg orally twice a day

**Higher doses are recommended for individuals with HIV**

CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137

**HSV and Pregnancy**

- May be transmitted to fetus **during pregnancy** or at **time of labor and delivery**
- **Suppressive therapy** from 36 weeks to delivery reduces the likelihood of lesions and viral shedding at the time of delivery
  - Acyclovir 400 mg TID
  - Valacyclovir 500 mg BID
  - Famciclovir 250 mg BID
- Careful examination of vulva and vagina recommended at the time of presentation in labor
  - If lesions, delivery by cesarean section recommended
  - If no lesions, may have a vaginal delivery

CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137

**Vaginitis/Vaginosis--Trichomonas Vaginalis**

- Anaerobic protozoan found only in lower genitourinary tract of humans
- Transmitted by sexual contact and has high rate of infectivity (80% of women with affected partner become infected)
- Cause of vaginitis in 5 to 50% of cases

CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137
Vaginitis/Vaginosis—Trichomonas vaginalis, con’t

- Risk factors:
  - Multiple partners, new partner
  - Frequent intercourse
  - Presence of another sexually transmitted infection

- Symptoms:
  - Asymptomatic in up to 50% of cases
  - Change or increase in vaginal discharge is most common symptom
  - Itching and/or dysuria may be present

- Signs:
  - Vaginal discharge, typically white, frothy (green, frothy in 10%)
  - Petechial hemorrhages of the cervix ("strawberry cervix") in 2 to 3%

- Diagnosis:
  - NAAT recommended
    - Sensitivity 95.3 – 100%, Specificity 95.2 – 100%
  - Saline wet mount of vaginal secretions
    - Sensitivity 51 – 65%
    - Shows
      - motile trichomonads in 80% of cases
      - > 10 WBC/hpf in most cases
      - pH of vagina is usually > 5
  - Culture
    - Sensitivity 75 – 90%, Specificity up to 100%
### Vaginitis/Vaginosis—Trichomonas vaginalis, con’t

- **Treatment:**
  - Metronidazole 2 grams orally as a single dose, or
  - Tinidazole 2 grams orally as a single dose, or
  - Metronidazole 500 mg orally twice a day for 7 days
  --may be used at any time during pregnancy

(CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64(RR-3), 1-137)

### Vaginitis/Vaginosis—Trichomonas vaginalis, con’t

- Sexual partners should be treated
- Offer testing for other sexually transmitted infections, including HIV
- Sexual activity should be avoided until patient and partner(s) are treated and asymptomatic
- No test of cure is needed if symptoms resolve

### Vaginitis/Vaginosis—Trichomonas Vaginalis, con’t

- **Significance:**
  - Bothersome symptoms
  - Increased incidence of upper genital tract infections, including salpingitis and salpingo-oophoritis, and post-operative infections after gynecologic procedures
  - Associated with an increased incidence of preterm delivery

### Vaginitis/Vaginosis—Bacterial Vaginosis

- Most common cause of vaginitis/vaginosis nationwide (15 – 50% of cases).
- **Characterized by:**
  - A shift in vaginal flora from predominance of Lactobacilli to mixed microbial population including Gardnerella vaginalis, anaerobes such as Peptostreptococci, Bacteroides, Prevotella, and Mobiluncus species, as well as mycoplasmas, which are present in increased numbers compared to the normal vagina.
  - A lack of hydrogen-peroxide producing Lactobacilli
  - A lack of inflammatory response
Vaginitis/Vaginosis—Bacterial Vaginosis, con’t

- Risk factors:
  - Sexual activity, multiple partners, new partner, female partner
  - Douching
  - African American background

- Symptoms:
  - Vaginal discharge, typically thin
  - Fishy vaginal odor
  - Vulvo-vaginal burning
  - Rarely, vulvo-vaginal pruritus

- Signs:
  - Thin gray-white vaginal discharge, often visible at the introitus

Vaginitis/Vaginosis—Bacterial Vaginosis, con’t

- Diagnosis:
  - Clinical diagnosis based on presence of 3 of 4 of Amna’s criteria:
    - Thin gray-white discharge
    - Presence of “clue cells” (epithelial cells studded with bacteria) on saline wet mount of vaginal secretions
    - Vaginal pH > 4.5
    - Positive “AMR” test (fishy odor) with addition of 10% potassium hydroxide to vaginal secretions
  - Sensitivity 62% and specificity 77% compared to Gram stain using Nugent’s criteria. Similar sensitivity and specificity noted in recent study using 2 of 4 criteria.

Vaginitis/Vaginosis—Bacterial Vaginosis, con’t

- Point of care tests for pH and amines, and proline iminopeptidase are commercially available
  - Role in diagnosis of bacterial vaginosis not yet well established

- For research purposes, Gram stain of vaginal discharge using Nugent’s criteria (weighted scoring system based on quantitation of Lactobacilli, Gardnerella and Bacteroides morphotypes, and Mobiluncus morphotypes).
Vaginitis/Vaginosis—Bacterial Vaginosis con’t

- **Treatment:**
  - Metronidazole 500 mg orally twice a day for 7 days, or
  - 0.75% Metronidazole gel, 5 grams intravaginally once a day for 5 days, or
  - Clindamycin cream 3%, one application (5 grams) intravaginally for 7 days
- **Alternatives:**
  - Tinidazole 2 grams orally once a day for 2 days, or
  - Tinidazole 1 gram orally once a day for 5 days, or
  - Clindamycin 300 mg orally twice a day for 7 days, or
  - Clindamycin 100 mg ovule intravaginally once a day for 3 days
- **Use may weaken condoms or contraceptive diaphragms**

CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64 (RR-3), 1-137

Vaginitis/Vaginosis—Bacterial Vaginosis, con’t

- **Significance** of diagnosis of bacterial vaginosis:
  - Unpleasant symptoms
  - Increased incidence of upper genital tract infections, including salpingitis-salpingitis and postoperative infections following gynecologic procedures
  - Increased likelihood of acquiring human immunodeficiency virus and herpes simplex virus
  - With pregnancy, associated with increased risk of spontaneous abortion and preterm delivery
Vaginitis/Vaginositis—Monilial Vulvovaginitis ("Yeast")

- Cause of vaginitis in 15 to 30% of cases.
- Characterized by increased numbers of fungi compared to the normal vagina and a significant inflammatory response with polymorphonuclear neutrophils.
- Caused by Candida albicans in most cases, and non-albicans species (e.g. Candida glabrata) in a small minority of cases.

Vaginitis/Vaginositis—Monilial Vulvovaginitis, con’t

- Risk factors:
  - Pregnancy, luteal phase of menstrual cycle
  - Recent treatment with broad-spectrum antibiotics
  - Use of spermicides
  - Young age (15 to 19 most common)
  - Diabetes mellitus, other conditions characterized by immunosuppression

- Symptoms:
  - Vulvovaginal pruritus, burning
  - Thick, curd-like, yellow-white vaginal discharge
  - Dyspareunia
  - Dysuria

Vaginitis/Vaginositis—Monilial Vulvovaginitis, con’t

- Signs:
  - Erythema of the vulva
  - Presence of erythematous papules at periphery of area of erythema ("satellite lesions")
  - Thick, curd-like, yellow-white vaginal discharge

- Diagnosis:
  - Presence of pseudohyphae and/or blastospores on saline wet mount or potassium hydroxide preparation of vaginal secretions (Sensitivity approximately 75% compared to culture)
  - Vaginal pH typically 3.8 – 4.5
  - Culture may be undertaken if pseudohyphae, blastospores are not seen microscopically

Diagnosis:
- Presence of pseudohyphae and/or blastospores on saline wet mount or potassium hydroxide preparation of vaginal secretions (Sensitivity approximately 75% compared to culture)
- Vaginal pH typically 3.8 – 4.5
- Culture may be undertaken if pseudohyphae, blastospores are not seen microscopically
Vaginitis/Vaginosis—Monilial Vulvovaginitis, con’t
• Treatment:
  • Candida albicans
    • Imidazole creams or suppositories intravaginally for 1 to 7 days.
    • Fluconazole 150 mg orally as a single-dose.
    • Topical combination of an antifungal agent and a steroid (e.g., miconazole and triamcinolone) may
      assist with vulvar symptoms.
  • Candida glabrata
    • Boric acid capsules 600 mg intravaginally once a day for 14 days.
• Patients who are pregnant, have uncontrolled diabetes mellitus, are immunosuppressed, or
  have recurrent episodes of Monilia, may require prolonged courses of treatment, a
  combination of intravaginal and oral treatment, and/or ongoing prophylaxis.

Self Treatment and Over-the-phone Treatment for Vulvo-vaginal symptoms
• Several studies have concluded that patient-reported symptoms and signs are not specific enough to make an accurate diagnosis of
  vulvovaginal infections.
  • Singh et al. compared a dx of Trichomonas, bacterial vaginosis, and vaginal candidiasis by questionnaire and patient-collected vaginal
    swab with a dx based on clinician-obtained history and exam
    • —Dx were missed in 34%, 32%, and 48% of cases respectively with
      questionnaire and pt-collected swab
  • Sex Transm Infect 2013; 89(3): 185-90

Case #1. Vulvo-vaginal Infections—Take home message
• Encourage patients with vulvo-vaginal symptoms to be seen for evaluation

Human Papillomavirus (HPV)
• Genital infections usually sexually-transmitted
• Infections may be subclinical or associated with exophytic and flat
  lesions (condylomata acuminata)
• Certain types associated with intraepithelial neoplasia
HPV Types and Genital and Extra-genital Disease

• Genital warts (condylomata accuminata)—Types 6 and 11
• Squamous intraepithelial lesions (SIL) and carcinoma of the cervix, vulva, vagina, anus, and penis—“high-risk” HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 8, 73, and 82
• HPV 16 found in 50% and HPV 18 found in 20% of cervical cancers
• Bowen’s disease—HPV 16, 18, 32, 33, 34, and others
• Squamous cell carcinoma of oral cavity—HPV 16
• Recurrent respiratory papillomatosis—HPV 6 and 11

HPV

• Condylomata acuminate

HPV--Treatment of external condylomata

• Patient applied:
  • Podofilox* 0.5% solution or gel, bid for 3 days, then none for 3 days, repeat for 4 cycles prn
  • Imiquimod* 5% cream or 5% cream hs twice a week for up to 16 weeks. Area should be washed 6–10 hrs. later
  • Sinecatechins* 15% ointment

• Clinician applied:
  • Cryotheraphy every 2-3 weeks prn
  • Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90% weekly prn
  • Surgical excision or Laser tx

*Should not be used during pregnancy
*May weaken condoms or vaginal diaphragms

(CDC Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR 64(RR-3), 1-137)
HPV—Additional Recommendations

• Offer screening for other sexually transmitted infections, including HIV
• Affected women and partners of affected men should be advised of the importance of regular Pap smears

HPV Vaccines

• Quadrivalent vaccine against HPV types 6, 11, 16, and 18 approved by FDA in 2006 (Gardasil). Bivalent vaccine against HPV types 16 and 18 was available in 2009 (Cervarix)
• Nonovalent vaccine against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil-9) now only HPV vaccine available in U.S.
  • Created from noninfectious virus-like particles of major capsid protein, L1
  • Trials show almost 100% efficacy in preventing clinical disease with included HPV types
  • Safety and efficacy demonstrated in individuals aged 9 to 26
  • Indicated for prophylaxis against cervical, vulvar, vaginal, and anal cancers as well as adenocarcinoma in situ of cervix, CIN 1, 2, and 3, VIN 2 and 3, VaIN 2 and 3, and anal warts caused by included HPV types

Gardasil-9

• Recommended for females and males aged 9 – 26
  • Females ages 9 to 26; encouraged at age 11 to 12, before onset of sexual activity
  • Can be given to postpartum women who are breastfeeding
  • Males ages 9 to 21, may be given until age 26
  • Recommended ages 22 – 26 if immunocompromised or MSM
• Standard regimen: 3 doses at 0, 2, and 6 months
  • If first dose given before age 15 and not immunocompromised, may give 2-dose regimen, with 2nd dose at 6 to 12 months
  • Ages 16 – 26 and immunocompromised individuals should receive 3-dose regimen

HPV Vaccines—Efficacy

• Since introduction in 2006, there has been a 64% decrease in infections with HPV types included in vaccines in teenage females in U.S.
• With 10 years of f/u, no decrease in protection noted

www.CDC.gov, 2017
Case #1. HPV—Take home message

• Encourage individuals ages 9 to 26 to receive the Gardasil-9 vaccine

Case #2

• A 30 year old nulligravid woman and her partner would like to conceive. Her partner traveled to Brazil for work 3 months ago and may have had a mosquito bite while there. He did not have any symptoms of an infection afterwards. Your patient has heard about the Zika virus and asks your advice about how to proceed.

Zika Virus

• Flavivirus related to dengue virus, yellow fever virus, and West Nile virus, that is transmitted by aedes aegypti mosquitoes.
• Since 2014, mosquito-borne infections have been noted in South America, the Caribbean, Miami-Dade County, Fl, and Brownsville, TX
• Symptoms occur in ~20% of infected individuals and include low-grade fever, conjunctivitis, maculopapular rash, and arthralgias (especially of hands and feet).
• Neurologic complications include Guillain barre syndrome, myelitis, and meningoencephalitis
Zika virus—Congenital Infection

- Congenital infections associated with:
  - Microcephaly, ventriculomegaly, cerebellar hypoplasia
  - Craniofacial malformations
  - Pulmonary hypoplasia
  - Cardiac septal defects
  - Contractures, arthrogryposis
  - Intrauterine growth restriction
  - Stillbirth

- The greatest risk of serious fetal sequelae occurs with infection in the first or second trimesters

Zika virus—CDC Recommendations for Pregnant Women

- Pregnant women
  - should not travel to areas with risk for Zika
  - if travel is essential, she should strictly follow steps to avoid mosquito bites and sexual transmission during and after travel
  - should avoid sex without a condom with a partner who has traveled to or lives in an area with Zika
  - with Zika symptoms and possible Zika exposure should be tested for infection
  - with no Zika symptoms but who have ongoing Zika exposure should be offered Zika testing
  - With possible exposure but no Zika symptoms and no ongoing exposure should not routinely be tested, but testing should be considered using a shared decision-making model

www.cdc.gov, 2017

Testing for Zika virus during Pregnancy

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommended Tests</th>
<th>Interpretation of Tests</th>
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</thead>
<tbody>
<tr>
<td>Exposure to and has symptoms of Zika</td>
<td>Serum and urine RNA nucleic acid testing (NAT) and Zika virus IgM.</td>
<td>If RNA NAT is neg and Zika IgM is pos, proceed with PRNT for Zika and Dengue.</td>
</tr>
<tr>
<td>Ongoing exposure to but no symptoms of Zika</td>
<td>Serum and urine RNA NAT testing 3 times during pregnancy.</td>
<td>Zika infection indicated by pos RNA NAT.</td>
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Zika virus—CDC Recommendations for Women and Men Planning to Conceive

- Avoid non-essential travel to areas with Zika
- Women and men with possible exposure to Zika and have symptoms of Zika should be tested
- Zika virus testing is not recommended for asymptomatic couples when one or both partners have had possible exposure to Zika
- Women and men diagnosed with Zika or who have had possible exposure to Zika through travel or sex should wait before attempting to conceive and use a condom during that time
- Men should wait at least 6 months
- Women should wait at least 2 months
- www.cdc.gov, 2017
Case #2. Response to patient’s question

- Encourage waiting until 6 months from the time of partner’s possible exposure to Zika to attempt to conceive and use a condom for the remainder of that time. If a condom is used, by the time 6 months has elapsed for her partner, the patient will be more than 2 months from her last possible exposure to Zika from her partner.
- Because the patient’s partner was asymptomatic, testing him for Zika is not recommended.