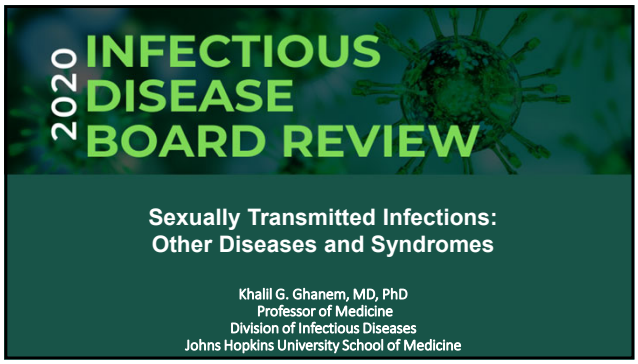
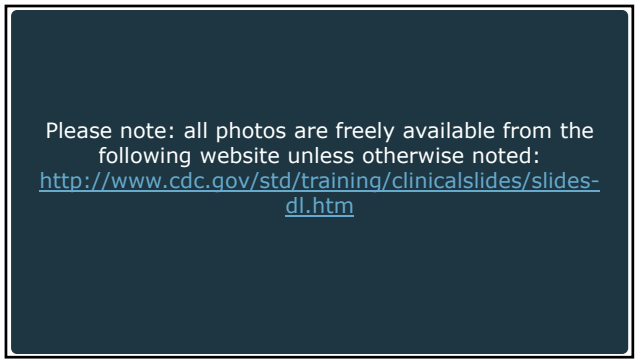
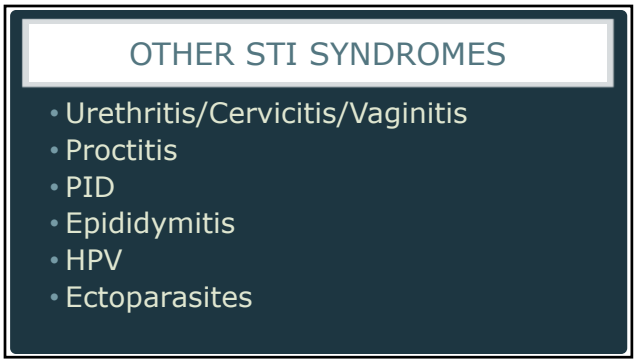
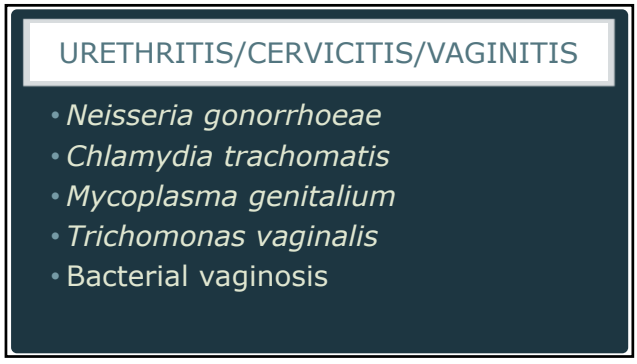
17 – Sexually Transmitted Infections: Other Diseases and Syndromes

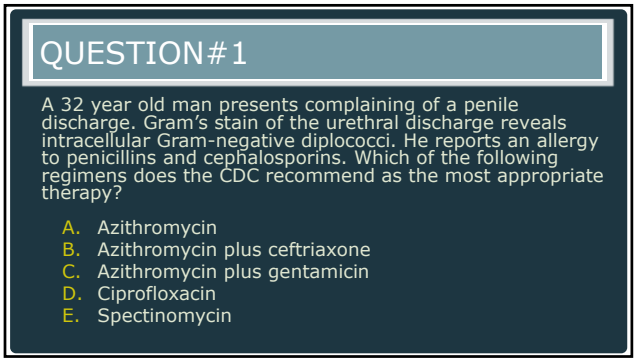
Speaker: Khalil Ghanem, MD











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QUESTION#2

Annual screening of which of the following STIs should be performed in HIV-infected but not in HIV-uninfected women?

A. Bacterial vaginosis
B. Chlamydia trachomatis
C. Neisseria gonorrhoeae
D. Herpes simplex virus
E. Trichomonas vaginalis

CHLAMYDIA TRACHOMATIS: TAKE-HOME POINTS

- Annual screening of all sexually active women aged ≤25 years is recommended for serotypes D-K, as is screening of older women with risk factors (e.g. new or multiple sex partners)
- High rate of reinfection for D-K
- Rectal LGV (L1-L3) has made a resurgence***
- Longer duration of therapy for L1-L3 serotypes **if symptomatic*****
- Association with reactive arthritis (Reiter's); prompt treatment reduces risk of reactive arthritis

CHLAMYDIA TRACHOMATIS

- Serological classification
  - A,B, Ba, C (Trachoma)
  - D-K (Genitourinary and ocular infections)
  - L1-L3 (Lymphogranuloma venereum)

CHLAMYDIA TRACHOMATIS D-K

MEN	WOMEN
• Asymptomatic	• Asymptomatic
• Urethritis	• Cervicitis
• Epididymitis (70% of cases in young men)	• Urethritis
• Proctitis	• **Pelvic inflammatory disease**
• Conjunctivitis	• Bartholinitis
• Pharyngitis (rare)	• Proctitis
• **Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)**	• Conjunctivitis
	• **Reactive arthritis**

CHLAMYDIA: DIAGNOSTICS

- Detection of WBCs on Gram's stain is not sensitive
- Cell culture (sensitivity 70%), direct immunofluorescence, non-amplified molecular tests (sensitivity ~85%), and NAATs (gold standard; sensitivity >95%; specificity >99%)
- FDA cleared for the detection of *C. trachomatis* on endocervical and urethral swab specimens, urine, vaginal swab specimens, throat and rectal swabs
- **Routine NAATs do NOT distinguish between D-K and L1-L3 serotypes. Multiplex tests do. The latter are not commercially available**

CHLAMYDIA TRACHOMATIS TREATMENT

- Duration of therapy depends on serotype:
  - D-K serotypes: Azithromycin 1g PO X1 OR **doxycycline 100mg PO BID X 7d**
  - L1-L3 serotypes (if symptomatic): **Doxycycline 100 mg PO BID X3 weeks** (preferred) OR Azithromycin 1g PO q week X 3 weeks
- Use of azithromycin is safe in pregnancy
- Test-of-cure (repeat testing 3–4 weeks after completing therapy) is **not** routinely recommended
- Screen all women treated for chlamydia infection 3 months later (REINFECTION rates are high)

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AZITHROMYCIN VS. DOXYCYCLINE

- **Urogenital** *C. trachomatis*
  - A metaanalysis of 23 RCTs: pooled efficacy difference in favor of doxycycline of 1.5% to 2.6% CID 2014; 59(2):193-205
  - Recent RCT in correctional facility: azithromycin=97% vs. doxycycline=100% (noninferiority of azithromycin was **not** established) NEJM 2015; 373;26:2513-2521
- **Rectal** *C. trachomatis*
  - A metaanalysis of 8 observational trials: pooled efficacy difference in favor of doxycycline of 19.9%

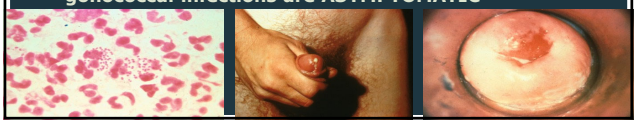
JAC 2015; doi:10.1093/jac/dku574

GONORRHEA: TAKE-HOME POINTS

- Drug resistance: dual therapy (ceftriaxone + azithromycin) is now the rule; NO FLUOROQUINOLONES
  - Macrolide resistance increasing!
- Pharyngeal gonorrhea: ceftriaxone and azithromycin have excellent efficacy; cefixime only 90% effective and spectinomycin only 70% effective
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone (not 250mg) plus azithromycin

NEISSERIA GONORRHOEAE

- Clinical presentation similar to that seen with *C. trachomatis*.
  - no association with Reiter's
  - responsible for 30% of cases of epididymitis in young men
  - **MOST cases (>90%) of pharyngeal and rectal gonococcal infections are ASYMPTOMATIC**



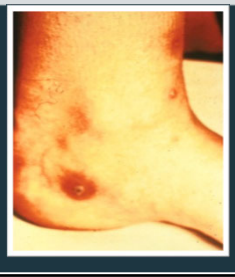
SCREENING FOR GONORRHEA

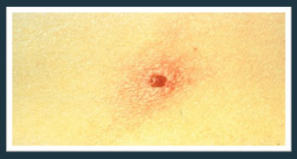
- HIV-infected men and women
- Sexually active MSM (**at all sites of exposure**)
- Individuals with new or multiple sexual partners
- Sexually active women <25
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted infections
- Women ≤35 and men ≤30 in correctional facilities at intake

DISSEMINATED GONOCOCCAL INFECTION (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions), asymmetrical arthralgia, tenosynovitis, or (monoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause minimal genital inflammation
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE)
- Differential diagnosis: meningococcemia, RMSF, dengue, staphylococcal endocarditis, Reiter's
- Treatment: Ceftriaxone IM/IV PLUS a single dose of azithromycin

DGI





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GONORRHEA DIAGNOSTICS

- A negative Gram's stain should NOT be considered sufficient for ruling out infection in **asymptomatic** men. In addition, Gram's stain of endocervical specimens, pharyngeal, or rectal specimens are not sufficiently sensitive or specific to detect infection
- Sensitivity of culture ~80-90% from endocervical or urethral specimens in symptomatic persons; <50% from throat/rectum
- NAATs offer the widest range of testing specimen types because they are FDA-cleared for use with endocervical swabs, **vaginal swabs**, male urethral swabs, and female and **male urine**
- NAATs are now FDA-cleared for specimens obtained from the rectum and pharynx; they are the 'tests of choice' for these sites

GONORRHEA THERAPY

- **Fluoroquinolones not recommended for the treatment of gonorrhea in the U.S.**
- The only first-line option is **ceftriaxone** (250mg IM x1) PLUS 1g PO azithromycin X1* (even if Chlamydia ruled out).
- High-level resistance to azithromycin emerging in the US
  - 4.6% of isolates in the US in 2018 had elevated MICs to azithromycin

***The use of azithromycin is likely to be abandoned in the next year; the dose of ceftriaxone MAY increase to 500mg IM**

GONORRHEA THERAPY (CONT.)

- **Second-line agents:**
  - **Cefixime (400mg PO X1) PLUS azithromycin**
  - **Gentamicin IM+ 2g azithromycin OR Gemifloxacin+ 2g azithromycin in persons with a cephalosporin allergy**
  - Azithromycin 2g PO X1 is **no longer recommended**
  - Cefixime is only 90% effective at eradicating pharyngeal infection
  - Emerging resistance to cephalosporins (particularly oral)
  - Gentamicin may have lower efficacy for pharyngeal infections (~80%) Ross JDC, et al. *Lancet* 2019
  - If any second-line regimen is used to treat pharyngeal infection, must do a test of cure within 2 weeks
  - Spectinomycin: Previous second-line agent; no longer available in the US; ~70% effective for pharyngeal infections

GONORRHEA THERAPY CONTINUED

- **DGI**: Ceftriaxone 1g IM or IV PLUS one dose of azithromycin until clinically better (can also use cefotaxime and ceftizoxime); then, can complete 7 day course of therapy with a PO cephalosporin (following antibiotic susceptibility testing)
- **Gonococcal conjunctivitis**: Ceftriaxone 1g IM X1 + azithromycin

EXTRAGENITAL GONORRHEA AND CHLAMYDIA

- 90% are asymptomatic
- NAATs, now FDA cleared, are the preferred (and most sensitive)diagnostic modality
- CDC recommends screening for both GC and CT in the rectum but screening for only GC in the throat
- Sexually active MSM should be screened at all sites of exposure
  - The majority of GC cases in MSM would be missed if genital-only testing were performed
- No formal screening guidelines for women

NON-GONOCOCCAL URETHRITIS (NGU)

- Gram stain of urethral secretions demonstrating ≥2 WBC per oil immersion field or positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBC per high power field
- More common etiologies:
  - *Chlamydia trachomatis* (25% cases)
  - *Mycoplasma genitalium* (30% of cases)
  - *Trichomonas vaginalis* (10-25% of cases)
  - *Ureaplasma urealyticum* (controversial)
  - HSV
- Less common etiologies: anaeobes; enterobacteriaceae, Haemophilus, *Staphylococcus saprophyticus*, adenovirus
- NGU treatment: Azithromycin 1g PO x1 OR **doxycycline 100mg PO BID X 7d***

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NON-GONOCOCCAL URETHRITIS (NGU) CONTINUED

- If a person with NGU fails to respond to therapy, think of 4 possibilities: (1) Reinfection (2) *M. genitalium* that did not respond to above therapy (see next slide) (3) *T. vaginalis*- rare in MSM (treat with metronidazole) or (4) HSV

MYCOPLASMA GENITALIUM

- Moderate to strong association with non-gonococcal urethritis (NGU) [up to 30% of cases] and up to 35% of cases of persistent urethritis
- Moderate association with cervicitis and PID; weaker association with infertility
- DRUG RESISTANCE
- FDA-cleared diagnostic test now available

M. GENITALIUM THERAPY

- Treatment with Azithromycin 1g PO X1 (success rate <50%) superior to doxycycline 100mg PO BID X 7days (success rate ~30%). Clin Infect Dis. 2015;61:1389–99
  - A longer course of azithromycin (an initial 500-mg dose followed by 250 mg daily for 4 days) ?better than single dose regimen
- **Moxifloxacin 400mg POX 7-14 days** if azithromycin fails PLoS One. 2008;3(11):e3618
  - Emerging resistance to fluoroquinolones (13.6% moxifloxacin resistance in a recent study) Emerg Infect Dis. 2017;23(5):809-812
- Pristinamycin was highly effective in treating macrolide- and quinolone-resistant strains Clin Infect Dis. 2015 ;60(8):1228-36

QUESTION #3

A 22 year old woman presents complaining of a vaginal discharge.

Her examination is remarkable for a gray homogenous discharge. A vaginal swab is obtained which reveals a pH>6.0, motile trichomonads, and the presence of 3 Amsel's criteria.

QUESTION #3

Which of the following is the most appropriate antimicrobial regimen for her and her partner?

	Patient	Partner
A	Metronidazole 2g X1	None
B	Metronidazole 2g X1	Metronidazole 2g X1
C	Metronidazole 1 week	None
D	Metronidazole 1 week	Metronidazole 2g X1
E	Metronidazole 1 week	Metronidazole 1 week

TRICHOMONAS VAGINALIS

- May be asymptomatic in both men and women; causes vaginitis and NGU
- Diagnosis: culture and PCR; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: metronidazole 2g PO X1 OR **tinidazole** 2g PO X1 OR metronidazole 500mg PO BID X 7 days [do NOT use topical gel formulations]
  - Recent clinical trial in HIV- women: 7 days of metronidazole superior to 2g single dose (but guidelines have not yet changed) Kissinger et al. Lancet Inf Dis 2019
- **Preferred Rx for HIV+ women: 7 days of metronidazole**
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance (see next slide)
- Partners in the preceding 60 days must be treated
- No need to screen asymptomatic pregnant women for trichomonas; **screen all HIV+ women annually**

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TRICHOMONAS & NITROIMIDAZOLES

- **Tinidazole** has a longer serum half-life and achieves higher tissue concentrations than metronidazole; MICs to tinidazole lower than to metronidazole
- If patient fails Rx with metronidazole 2g PO X1 & reinfection is excluded:
  - Option 1: Tinidazole 2 g PO X1
  - Option 2: Metronidazole 500mg PO BID X 7d
- If patients fails either option 1 or 2 above:
  - Option 3: Metronidazole 2g PO QD X 5d
  - Option 4: Tinidazole 2g PO QD X 5d

BACTERIAL VAGINOSIS

- Complex polymicrobial infection; causes vaginitis (thin, white, discharge with 'fishy' odor) and cervicitis; may increase risk of PID
- May be sexually-associated but not a STD; partners do NOT need to be treated
- Dx: Nugent's score preferred in research settings; Amsel's clinical criteria performed in clinical settings:(1) discharge (2)pH>4.5 (3) clue cells (4) amine odor with KOH (whiff test)

BACTERIAL VAGINOSIS

- Rx: Metronidazole 500mg PO BID X 7days OR Clindamycin 300mg PO TID X 7 days OR topical metronidazole gel or clindamycin cream
  - *L crispatus* supplements after topical metronidazole resulted in a 34% reduction in recurrence at 3m Cohen NEJM 2020
- **Do NOT use metronidazole 2g PO X1**
- **BV during pregnancy:** associated with preterm labor, PROM, post-partum endometritis
- Treat all **symptomatic** cases of BV during pregnancy; **screen asymptomatic pregnant women for BV ONLY if high risk for pre-term delivery (e.g. history of premature delivery)**

PELVIC INFLAMMATORY DISEASE (PID)

- Diagnostic criteria- only ONE of the following:
  - Cervical motion tenderness
  - Uterine tenderness
  - Adnexal tenderness
- Hospitalize
  - Pregnant
  - Tubo-ovarian abscess
  - Appendicitis cannot be excluded
  - Did not respond to PO antibiotics
  - Patient has nausea and vomiting, or high fevers/severe illness
  - Unreliable follow-up if treated as outpatient
- MOST patients with PID can be treated as outpatients (including first-episode PID and HIV positive women who do not meet above criteria)

PELVIC INFLAMMATORY DISEASE (PID)

- **THERAPY**
  - **Ceftriaxone** 250 mg IM in a single dose **PLUS Doxycycline** 100 mg orally twice a day for 14 days **WITH OR WITHOUT Metronidazole** 500 mg orally twice a day for 14 days
  - **Cefotetan** 2 g IV every 12 hours **OR Cefoxitin** 2 g IV every 6 hours **PLUS Doxycycline** 100 mg orally or IV every 12 hours
- Additional recommended regimens can be found at:

  http://www.cdc.gov/std/tg2015/pid.htm
- All patients treated with PO regimens should improve within 3 days otherwise, admit for parenteral antibiotics
- Treat all sex partners in preceding 60 days

FITZHUGH-CURTIS SYNDROME

- Perihepatitis: RUQ pain or pleuritic pain; usually NO LFT abnormalities (or very mild)
- Complicates ~10% of PID cases
- Pathophysiology: ?Direct extension of pathogens vs. immunological mechanism
- Rx: NSAIDs (+ treat PID)

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EPIDIDYMITIS

- In young men:
  - *C. trachomatis* (70%)
  - *N. gonorrhoeae* (30%)
- In older men: *E. coli* causes majority of cases
- Therapy:
  - **Ceftriaxone 250mg IM X1 + Doxycycline 100mg PO BID X 10 days**
  - For acute epididymitis most likely caused by sexually-transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex): Ceftriaxone IM X1 + levofloxacin X 10 days
  - For acute epididymitis most likely caused by enteric organisms: Levofloxacin 500mg PO X10 days

QUESTION #4

A 30 year old HIV+ man presents with severe pain on defecation and bloody anal discharge. He had unprotected anal sex one week ago. He experiences pain with DRE. There are no visible anal ulcers but a bloody mucoid anal discharge is noted. No diagnostic tests are available.

Which of the following empiric antibiotic regimens is most appropriate?

A. Ceftriaxone 250mg IM + Azithromycin 1g PO X1
B. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 7d
C. Ceftriaxone 250mg IM + Azithromycin 1g PO weekly X 3wks
D. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 21d
E. Ceftriaxone 250mg IM + Doxycycline 100mg PO BID X 7d + oral valacyclovir

PROCTITIS/ PROCTOCOLITIS

COMMON

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis* D-K
- *Chlamydia trachomatis* L1-L3 (LGV)
- *T. pallidum*
- HSV (severe especially among HIV+)

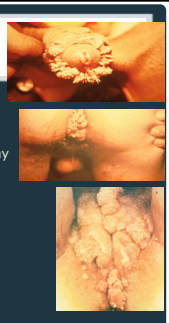
OTHER CAUSES

- Campylobacter
- Shigella
- Entamoeba
- CMV
- *Giardia lamblia** (mainly enteritis; especially among MSM)

PROCTITIS THERAPY

- **Ceftriaxone 250mg IM X1 + Doxycycline 100mg PO BID X 7 days**
- Treat for LGV: Bloody discharge, perianal ulcers, or mucosal ulcers among MSM with acute proctitis and either a positive rectal chlamydia NAAT or HIV infection
- Treat for HSV: Painful perianal ulcers or mucosal ulcers are detected on anoscopy
- Azithromycin may be less effective than doxycycline when treating proctitis due to *C. trachomatis*.

HPV



- >30 types cause genital infections
- High risk (e.g. 16, 18) and low-risk (e.g. 6 &11)
- 16 & 18 cause ~70% of cervical cancers in addition to significant proportion of vulvar, vaginal, anal, and upper airway cancers
- Low-risk types can cause genital warts and low-grade dysplasia (CIN I)
- Low-risk types cause recurrent respiratory papillomatosis
- Single biggest risk factor for dysplasia is PERSISTENCE of infection
- Risk factors for persistence: older age; immunosuppression; smoking; concurrent infection with multiple types

GENITAL WARTS

- 90% of warts caused by HPV 6 & 11; concomitant infection with types 16, 18, 31, 33, and 35 increases risk of HSIL
- Genital warts may develop months or years after infection
- Up to 60% of warts will recur within 3 months after therapy. Many will clear spontaneously after 12 months
- Available therapies do not completely eradicate infectivity
- Hypopigmentation or hyperpigmentation can occur with ablative modalities (cryotherapy and electrocautery) and with immune modulating therapies (imiquimod).
- No c-section in pregnant women with visible warts
  - C-section only if the warts are obstructing the birth canal or if vaginal delivery may lead to increased risk of bleeding

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HPV VACCINES

- **Nonavalent (6, 11, 16, 18, 31, 33, 45, 52, 58)**; 2-3 doses given over 6-12 months (2 doses induce good immunity if age<=14 years)
- Consists of VIRUS-LIKE PARTICLES (**noninfectious**; NO DNA)
- Efficacy: >97% against CIN 2/3, vulvar, and vaginal lesions; >98% against genital warts*
- Recommended for routine use in 9 to 26 year old women (even those who have a history of abnormal Pap smears); routine use in boys ages 11-12 years, catch-up for males ages 13-21, and permissive use of the vaccine in men ages 22-26; vaccine FDA cleared for women up to age of 45 (but ACIP has not recommended it in women age>26)

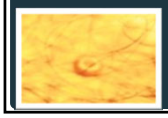
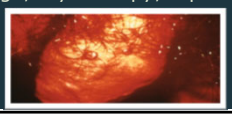
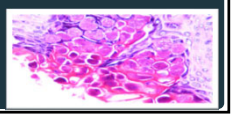
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

HPV VACCINES (CON'T.)

- Do not give during pregnancy; no need to restart schedule for patients who don't follow-up on time: JUST PICK UP WHERE YOU LEFT OFF
- Continue routine Pap smears on all women who get the vaccine
- Side effects: vasovagal response; local reactions
- Not a therapeutic vaccine

MOLLUSCUM CONTAGIOSUM

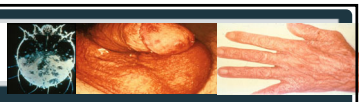
- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

PEDICULOSIS PUBIS

- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion or Ivermectin in case of treatment failure
  - Do NOT use Lindane; toxicities include seizures and aplastic anemia
  - Treat sex partners within previous 30 days


SCABIES



- *Sarcoptes scabei*
- Severe pruritus; especially at night or after bathing; burrows; the diagnosis is usually a clinical one
  - Permethrin cream 5% (wash off after 8 hours) OR
  - Ivermectin 200 mcg/kg PO day 1 and 14
  - Only use Lindane as an alternative
- **Crusted scabies** or 'Norwegian scabies'
  - **Mainly occurs in immunodeficient patients (HIV)**
  - **May NOT cause pruritus or burrows**
  - Contagious and aggressive
  - **Ivermectin 250mcg/kg on days 1, 15, and 29**
- Rash and pruritus of scabies may persist for up to 2 weeks after successful therapy***

Arch Dermatol. 2007;143(5):626

THE END