Sexually Transmitted Infections

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INFECTIOUS DISEASES

Learning Objectives

- USPSTF guidelines for STI screening
- Review symptoms, diagnostic strategy and treatment for:
  - Syphilis
  - Neisseria gonorrhoeae/DGI
  - Chlamydia trachomatis/LGV
  - HSV
  - Pelvic Inflammatory Disease (PID)
  - Epididymitis

Disclosures

- I have nothing to disclose

U.S. Preventive Services Task Force

- GC/C:
  - sexually active females <24yo and older women at increased risk for infection
- HIV:
  - all pregnant women
  - 15-65 yo and those younger or older who are at increased risk of infection
- Syphilis
  - All pregnant women
  - Asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection

Genital Ulcer Diseases (GUD)

- Syphilis (Treponema pallidum)
- HSV-2
- HSV-1
- Chancroid (Haemophilus ducreyi)
- Lymphogranuloma venereum (LGV) (Chlamydia trachomatis)
- Granuloma inguinale (Donovanosis) (Klebsiella granulomatis)

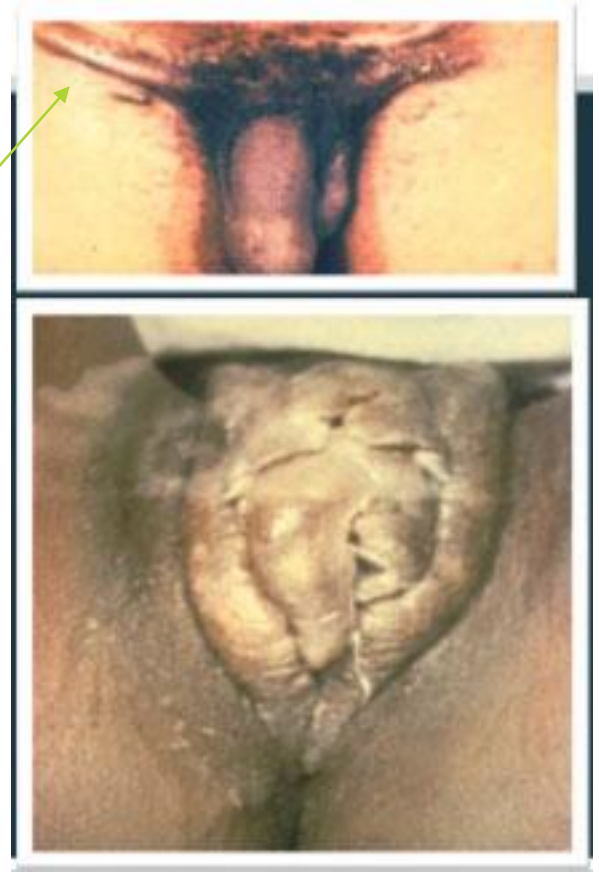
Which ulcers are Painful?	Which ulcers are Painless?
HSV Chancroid	Syphilis* LGV (but lymphadenopathy is Painful) Granuloma inguinale

* > 30% of patients have multiple painful lesions

"Key Words"

- Syphilis: Single, **painless** ulcer or chancre at the inoculation site with heaped-up borders and clean base; painless bilateral LAD
- HSV: multiple, **painful**, superficial, vesicular or ulcerative lesions with erythematous base
- Chancroid: painful, indurated, 'ragged' genital ulcers and tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- GI: **Painless,** progressive (destructive), **"serpiginous"** ulcerative lesions, without regional lymphadenopathy; beefy red with white border and highly vascular
- LGV: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy; "groove sign"**

Groove sign



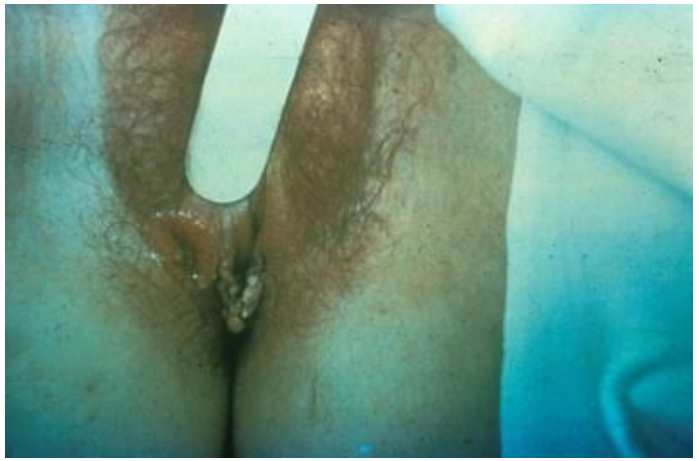
Genital elephantiasis (chronic)

Question 1

35 yo F presents with painless ulcer on her vulva and her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms. PE: reveals 2 ulcers with heaped-up borders and a clean base.

What is the most likely diagnosis?

A. HSV
B. Chancroid
C. LGV
D. Primary Syphilis
E. Secondary Syphilis



https://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

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Primary syphilis

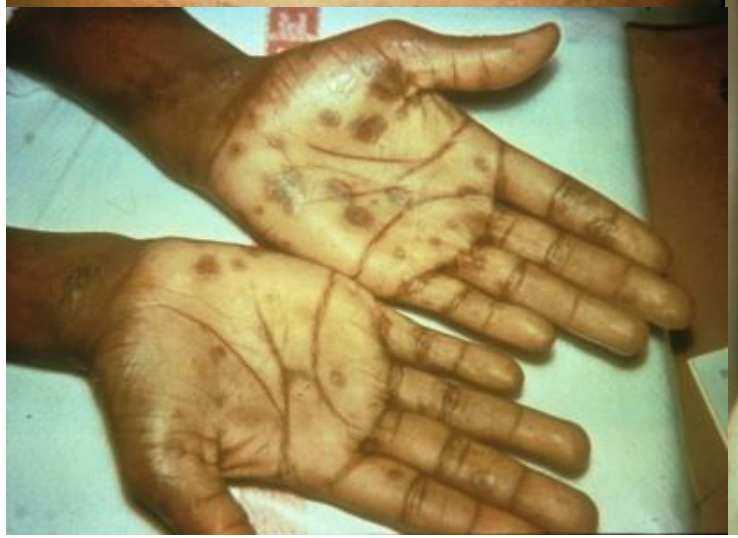
- Chancre occurs at point of introduction/contact 10-90 days (average 3 weeks) after exposure
  - Begins as a papule, quickly ulcerates to form a single, painless, clean based ulcer with indurated edges
  - Patient is highly infectious at this time
  - Most common location of lesion(s):
    - Penis: (heterosexual men) and men engaging in anal insertive intercourse
    - Labia, cervix: most commonly seen in women
    - Chancre occurs at the site of inoculation therefore can be seen in many locations: anal canal, mouth, eyelid, etc.
    - Untreated, lesion(s) spontaneously heal in 3-6 wks without a scar
    - Chancre often missed if occurring on the cervix or if intra-anal
- Regional lymphadenopathy: unilateral or bilateral, often found if sought

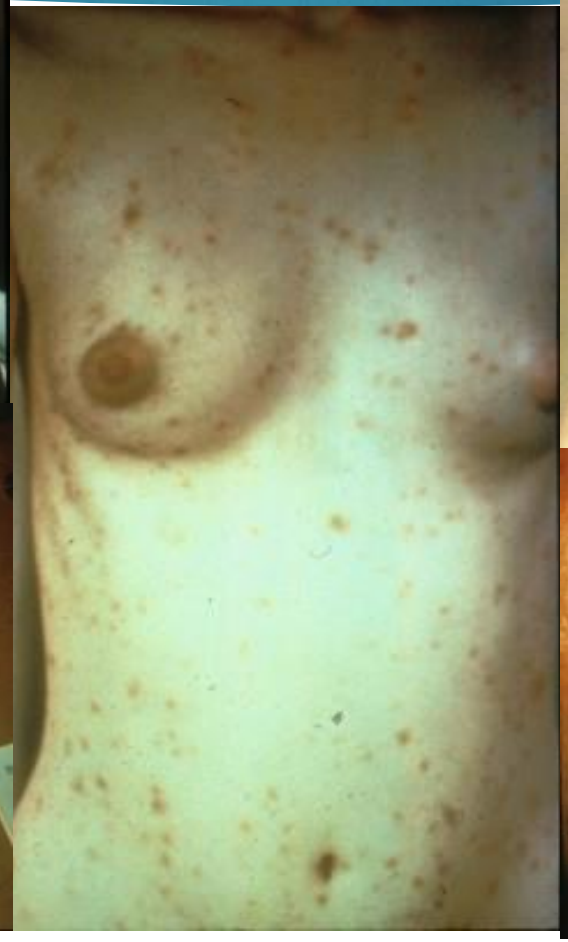
Secondary Syphilis

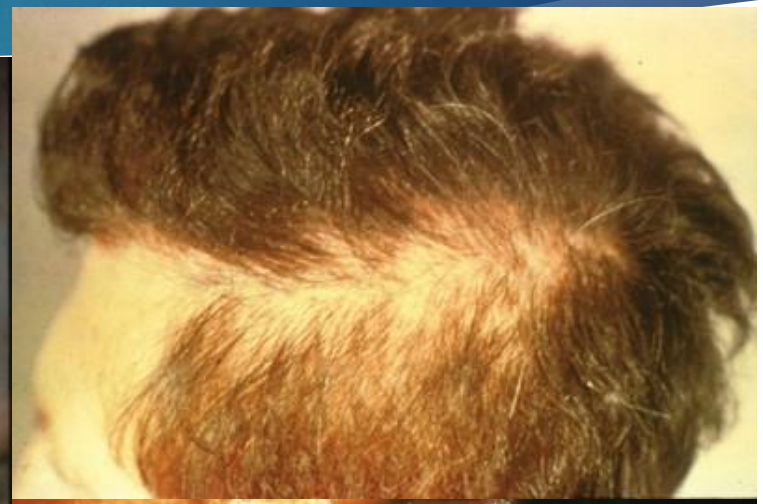
Highly varied lesions in appearance and location

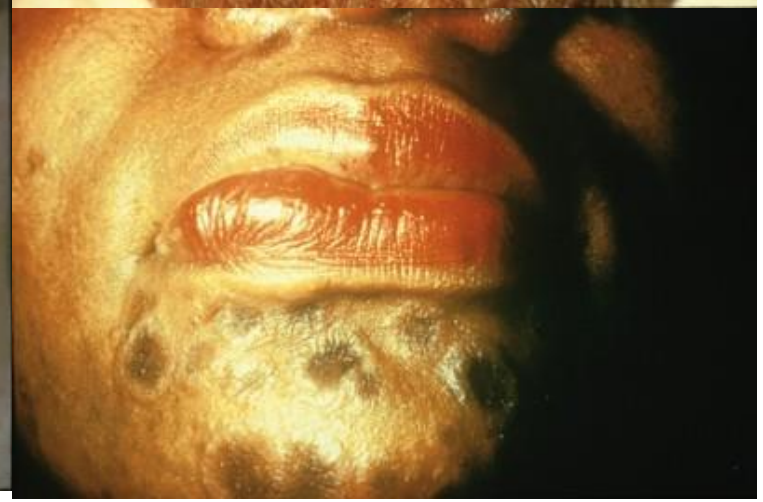
- Classic rash is the so-called "copper penny" macular lesions on the palms and/or soles
  - Rash can be generalized or focal as well as macular, popular, pustular or a combination
  - Usually non-pruritic and painless
- Mucous-membrane related lesions include condylomata lata (papillomatous-appearing, heaped-up lesions) and mucous patches occurring in the mouth, vagina, labia and glans penis
  - Condylomata lata are most commonly seen in warm, moist area of the body – intertriginous zones. These lesions are teaming with spirochetes
- Constitutional symptoms: fever, headache, general malaise, sore throat, anorexia, and occasionally, meningismus.
- Less common manifestations: proctitis, hepatitis, nephritis, arthritis, uveitis and other eye findings, meningitis
- Generalized lymphadenopathy is usually present at this stage. Dark field microscopy of lymph node aspirate is positive and diagnostic.
- Onset up to 6 months following exposure, usually after primary lesions have healed
- Highly infectious at this stage
- Lesions will heal spontaneously even if untreated

Secondary Syphilis









Neurological Manifestations of Syphilis

- Can occur during any stage of infection
- Can be asymptomatic or symptomatic
- Symptomatic early neurosyphilis
  - Occurs within the first year after infection
  - Mainly among HIV+ persons
  - Presents as meningitis (headache; photophobia; cranial nerve abnormalities; ocular symptoms)
- Symptomatic late neurosyphilis (tertiary syphilis)
  - Usually occurs ~10 years AFTER primary infection
  - Divided into 2 categories
    - Meningovascular (can present as stroke)
    - Parenchymatous

Neurosyphilis

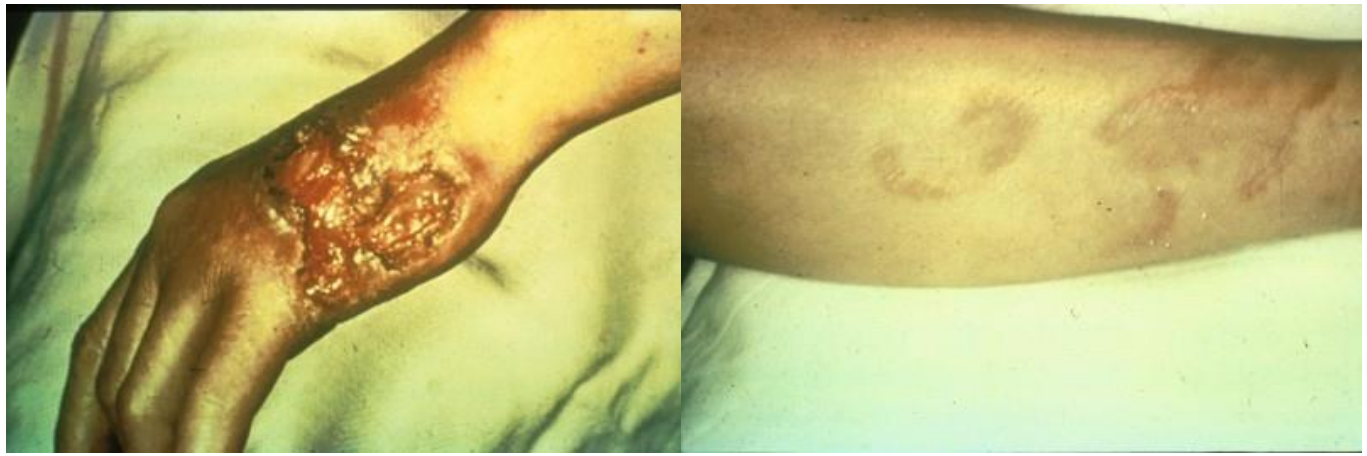
- Perform CSF exam and serology on all suspect cases
- Typical CSF findings: pleocytosis (>5 WBC/mL), elevated protein, decreased glucose, or a reactive CSF Venereal Disease Research Laboratory (VDRL) * *highly specific but not very sensitive (~50%)*

Late Neurosyphilis (Tertiary)

Meningovascular	Parenchymatous
• Endarteritis of the small blood vessels of the meninges, brain, and spinal cord. • Typical clinical manifestations include strokes (middle cerebral artery distribution is classic) and seizures	• Due to actual destruction of nerve cells • Tabes Dorsalis: shooting pains, ataxia, cranial nerve abnormalities; optic atrophy • General paresis: dementia, psychosis, slurring speech; Argyll Robertson pupil

Other Tertiary Manifestations

Cardiovascular	Late benign syphilis
• 15-30 years after latency • Men 3x>women • Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis	• 'Gummas' • Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)



Syphilis: Eyes and Ears

Eyes	Ears
• Ocular manifestations may occur during any stage and may involve any portion of the eye • Uveitis and neuroretinitis: mainly secondary stage • Considered a subset of neurosyphilis for management purposes	• Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, ringing or vertigo) • CSF exam is normal in >90% of cases of otic syphilis

Syphilis Serological Testing

Nontreponemal tests	Treponemal tests
• RPR and VDRL • May be used as screening test • False +: endemic treponematoses, old age, pregnancy, autoimmune disease, viral infections • Reactive results must be confirmed with treponemal test • False negative: Prozone effect • Four-fold (i.e. 2-dilution) decline after treatment=CURE	• MHA-TP, TPPA, FTA-Abs, EIAs, CIA • Detect IgG +/- IgM antibodies against treponemal antigens • Usually used as confirmatory test if nontreponemal test reactive • Once reactive, always reactive • False + may occur with endemic treponemal infections (e.g. yaws, pinta, bejel) or with Lyme disease

Testing Algorithms

If a patient has a positive Treponemal test/TPPA and a negative RPR what could this mean?

A. The patient had syphilis in the past and was adequately treated
B. The patient had syphilis in the past and was NOT adequately treated
C. Prozone reaction in secondary syphilis
D. All of the above

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Prozone Phenomenon

- A false-negative response arising from cases in which high antibody titers interfere with the antigen-antibody lattice network formation that is necessary for visualizing a positive flocculation test.
- The prozone phenomenon typically occurs when undiluted serum is used

Syphilis: Diagnostics

- Definitive diagnosis requires direct identification of the organism from a sample (i.e. Darkfield microscopy seen at the right). We reach a presumptive diagnosis via serology.
- Darkfield microscopy for genital ulcers of primary syphilis; sensitivity of serology in primary syphilis only~70%
- Sensitivity of serology for secondary or early latent syphilis ~100%
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life*
- No single test can be used to diagnose neurosyphilis
  - 50% of neurosyphilis cases may have negative CSF VDRL; it is highly specific, but insensitive
  - ~30% of persons with LATE neurosyphilis may have nonreactive SERUM nontreponemal test

Syphilis Therapy

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID x 14 days
- Late latent/unknown duration
  - 2.4 MU of long acting benzathine penicillin G IM x 3 (over 2 weeks) or doxycycline 100mg PO BID x 4 weeks
- Neurosyphilis/Ocular syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days (4 million units q4h IV x 14 days)
  - Ceftriaxone 1-2g IV/IM X 10-14 days (if PCN allergy and not pregnant)
- Jarisch-Herxheimer:
  - an acute febrile reaction often accompanied by headache, myalgia, and rash within 6 hours (up to 24 hours) after therapy
  - Typically occurs in early syphilis with higher infectious burden
  - antipyretics only
  - may induce early labor

Question 2

A pregnant female presents with a diffuse rash. On exam, she has a temperature to 38.3°C and a macular rash on her trunk and extremities including her palms. Serum RPR is reactive at a titer of 1:2048 and FTA-ABS is reactive. She has a history of severe hives to penicillin but has tolerated cephalosporins.

Which of the following antibiotics is most appropriate?

A. Azithromycin
B. Benzathine penicillin G
C. Ceftriaxone
D. Doxycycline

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Syphilis and Pregnancy

- Screen all women at 1st prenatal visit
- Screen all high risk women and those women living in high prevalence areas twice in the 3rd trimester: at 28-32 weeks and again at the time of delivery
- Screen all women who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic women with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

Syphilis and HIV

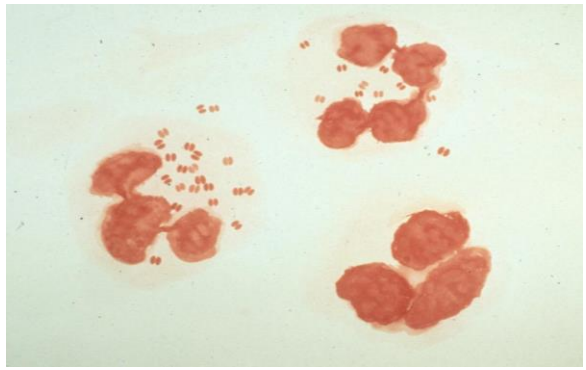
- Clinical manifestations similar but timeline may be compressed
  - HIV+ patients more susceptible to early neurosyphilis
- Testing and therapy similar to HIV-uninfected
- Follow-up is more frequent (every 3 months)

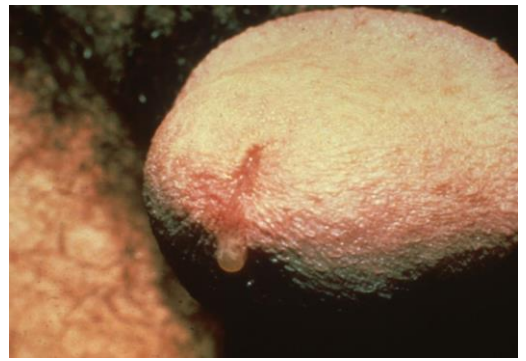
Question 3

32 yo M presents with penile discharge. Gram stain of the urethral discharge reveals intracellular Gram-negative diplococci.

Which of the following regimens does the CDC recommend as the most appropriate therapy?

A. Azithromycin
B. Azithromycin plus ceftriaxone
C. Azithromycin plus gentamicin
D. Ciprofloxacin
E. Spectinomycin





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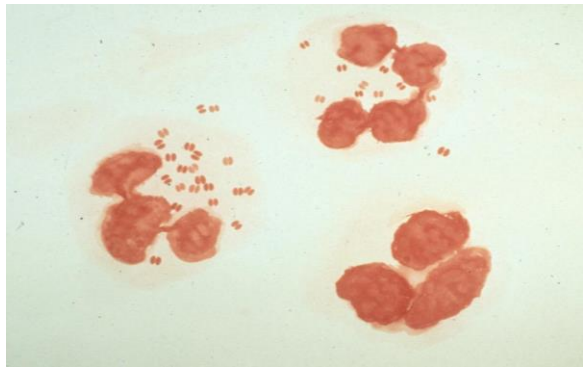
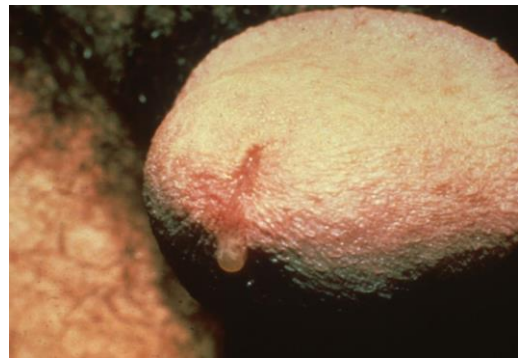




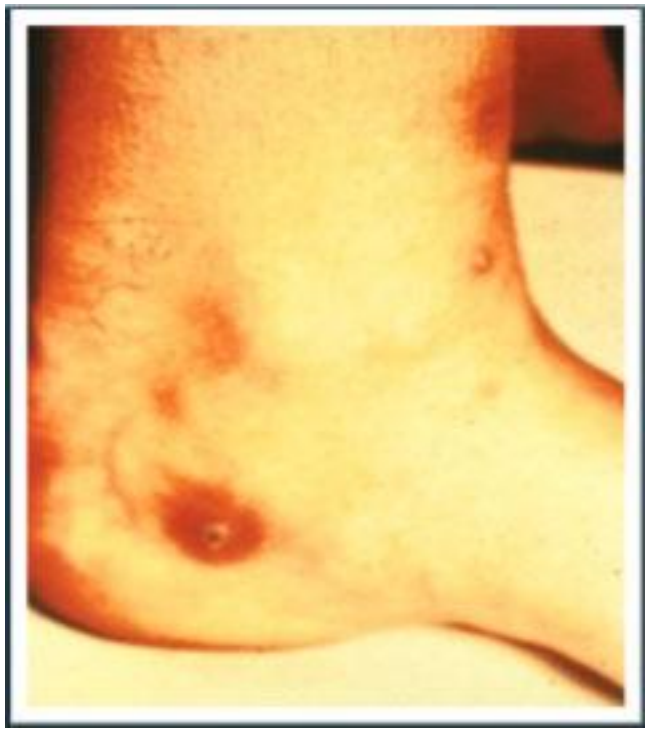
Neisseria gonorrhoeae

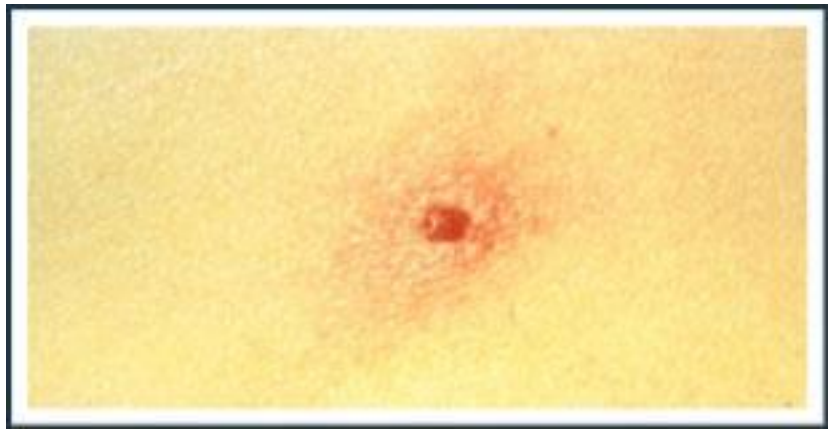
- Gram-negative diplococcus, oxidase and catalase positive
- Always considered pathogenic when identified
- In men:
  - Symptomatic urethritis, but up to 25% of infections are asymptomatic
  - Epididymitis is the most frequent complication in men (30%)
- In women:
  - Up to 50% of infections are asymptomatic
  - In women, accessory gland infection, perihepatitis, perinatal morbidity, and PID
- In both:
  - Anorectal infection, pharyngitis, conjunctivitis and disseminated infection

Neisseria gonorrhoeae

- Incubation period is 3-7 days in men; unclear in women but maybe 10 days
- Disseminated gonococcal infection occurs in 0.5-3% of gonorrhea cases
  - Presents with skin lesions (macules, papules, bullae, erythema nodosum), tenosynovitis, polyarthralgia, or septic arthritis
    - Positive BC in 50% of cases presenting with tenosynovitis or polyarthralgia, but rare in septic arthritis cases
  - Most patients with DGI have no symptoms of gonorrhea at mucosal sites

Disseminated gonococcal infection





Neisseria gonorrhoeae- Diagnostics

- Culture is no longer the diagnostic standard (only preferred if dx unclear when treatment failure is a concern)
- Gram stain of male urethral specimen that shows PMNs with intracellular gram-negative diplococci is sufficient for diagnosis; however a negative gram stain is not sufficient to rule out infection in asymptomatic men (due to low sensitivity)
- Nucleic acid amplification test (NAATs): method of choice to detect CT/GC urogenital infection in both men and women with and without symptoms
  - Optimal specimens are vaginal or endocervical (if pelvic exam performed), and first urine catch in men (in women may miss up to 10%)
  - Recommend for extragenital sites
  - Superior to culture and non-culture diagnostic methods

Neisseria gonorrhoeae- Diagnostics

- Test of cure
  - Test of cure not needed for persons with uncomplicated urogenital or rectal gonorrhea
  - Recommended for any person with pharyngeal gonorrhea who is treated with an alternative regimen
    - Should return 14 days after treatment for a test of cure using either culture or NAAT.

Gonorrhea Therapy

Standard of care = 2 drug regimen to treat co-occurring chlamydia and to hinder spread of cephalosporin resistance

- The only first-line option is ceftriaxone (250mg IM x 1) + 1g PO azithromycin x 1 (even if Chlamydia ruled out) **High-level resistance to azithromycin emerging in the U.S.*
  - **Fluoroquinolones not recommended for the treatment of gonorrhea in the U.S.**
- 2nd line agents (must do a test for cure within 2 wks):
  - Cefixime 400mg po x1+ azithromycin
  - Gentamicin IM + 2g azithromycin (or Gemifloxacin + 2g azithro) in those with cephalosporin allergy
- DGI
  - Ceftriaxone 1g IV q24h + azithromycin 1g PO x 1 (continued 24-48hrs after improvement begins at which time therapy may be switched to complete at least 1 week of therapy but may be longer)
- Gonococcal conjunctivitis: Ceftriaxone 1g IM X1 + azithromycin

Counseling - No sex for 7 days

Treat partners – 30-70% infected

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 STIs
- Women<35 and men <30 in correctional facilities at intake

Neisseria gonorrhoeae-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
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone (not 250mg) plus azithromycin

Chlamydia trachomatis (D-K)

Men	Women
• Asymptomatic • Urethritis • Epididymitis (70% of cases in young men) • Proctitis • Conjunctivitis • Pharyngitis (rare) • Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)	• Asymptomatic • Cervicitis • Urethritis • Pelvic Inflammatory Disease • Bartholinitis • Proctitis • Conjunctivitis • Reactive arthritis

Chlamydia Trachomatis L1-L3: Lymphogranuloma venereum (LGV)

- Classic manifestation is a short-lived painless genital ulcer accompanied by painful inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with proctitis particularly among MSM
  - Rectal pain, tenesmus, rectal bleeding/discharge
  - May be mistaken for inflammatory bowel disease histologically (early syphilitic proctitis may also be mistaken for IBD on histology)

Chlamydia trachomatis

- NAAT – gold standard (sensitivity>95%; specificity>99%)
- FDA cleared for the detection of C. trachomatis on endocervical and urethral swab specimens, urine, and vaginal swab specimens
- Routine molecular tests do NOT distinguish between D-K and L1-L3 serotypes. Multiplex PCR can be performed for specific serotypes.

Chlamydia trachomatis

- Duration of therapy depends on serotype:
  - D-K serotypes: azithromycin 1g PO x 1 or doxycycline 100mg PO BID x 7 days
  - L1-L3 serotypes: Doxycycline 100mg PO BID x 3 weeks (preferred) or Azithromycin 1g PO qweek x 3 weeks
- Use of azithromycin is safe in pregnancy
- Screen all women treated for chlamydia infection 3 months later (reinfection rates are high)

Chlamydia Trachomatis: Take Home Points

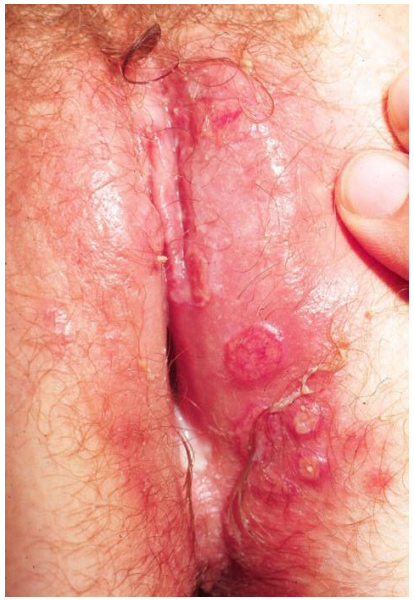
- Annual screening of all sexually active women aged <25 years is recommended for serotypes D-K, as is screening for older women with risk factors (e.g. new or multiple sex partners)
- High rate of reinfection for D-K
- Drug resistance (doxycycline, azithromycin) is uncommon but reported
- Rectal LGV (L1-L3) has made a resurgence
- Longer duration of therapy for L1-L3 serotypes
- Association with reactive arthritis (Reiter's)

Question 4

A 30 yo woman comes to see you in clinic complaining of painful lesions on her labia for 4 days. She is concerned she has herpes. She has been married for 2 years, and has had no other partners. She believes her husband is also monogamous, but is now questioning that.

What is the best test?

A. Obtain endocervical swab for Chlamydia
B. Send fluid from lesion for viral culture and HSV PCR
C. Obtain Urine for GC/C
D. Obtain vaginal swab to look for clue cells
E. Send serum RPR



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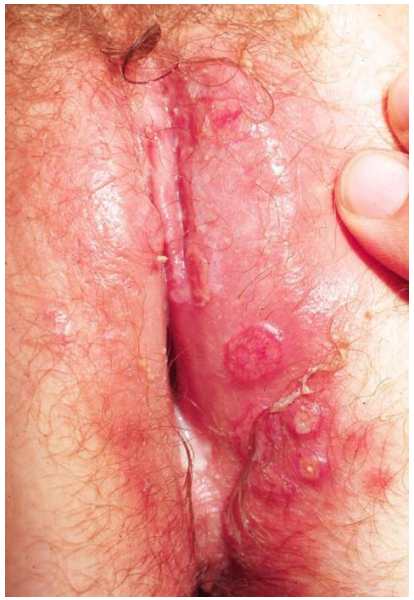

Herpes Simplex Virus (HSV)

- Both HSV-1 and HSV-2 cause genital disease
- HSV-1 is now becoming a more frequent cause of genital disease (especially in young women and MSM)
- In general, HSV-1 recurrences are less severe and less frequent and asymptomatic shedding is less frequent
- Prior infection with HSV-1 may attenuate severity of HSV-2 infection
- Classical presentation of multiple, painful, superficial, vesicular or ulcerative lesions with erythematous base may be absent

HSV: Diagnostics

Patient presents with genital ulcer

- Tzanck smear (40% sensitive)
- Culture (sensitivity 30-80%) "gold standard"
  - Obtain scraping of cells, or fluid by unroofing intact blister with sterile needle
- Antigen detection (70% sensitive)
- PCR (FDA cleared, >90% sensitive, 97% specific)

HSV treatment

- First clinical episode: Acyclovir, Famciclovir or Valacyclovir for 5-10 days
- Episodic rx for recurrences: self administered therapy when an outbreak arises
- Suppressive daily therapy for recurrent disease
  - Acyclovir 400mg PO BID or 400-800mg PO 2-3x daily (HIV positive)
  - Famciclovir 250mg PO BID or 500mg PO BID (HIV positive)
  - Valacyclovir 500mg PO daily
  - Valacyclovir 1g PO Daily (in >10 recurrences/year)

HSV and Pregnancy

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery= 30->50%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- A woman with a history of HSV who does NOT have ACTIVE lesions at time of delivery can deliver vaginally. C-sections are recommended ONLY IF ACTIVE LESION PRESENT AT DELIVERY
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking. Currently, no formal recommendations exist.

HSV Take-Home

- Both HSV-1 (particularly among young women and MSM) and - 2 cause genital infections
- Most people are unaware that they are infected
- Asymptomatic shedding is the most common reason for transmission
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations
- C-section ONLY in women who have active lesions at the time of delivery

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 x 1 or tinidazole 2g PO x 1 or metronidazole 500mg PO BID x 7 days

- **Preferred Rx for HIV+ women: 7 days of metronidazole**
- Partners in the preceding 60 days must be treated

No need to screen asymptomatic pregnant women for trichomonas; **screen all HIV+ women annually**

Pelvic Inflammatory Disease (PID)

- Diagnostic criteria (only 1 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 outpatient (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 + Doxycycline 100mg PO BID x 14 days with or without Metrondiazole 500mg PO BID x 14 days
  - Cefotetan 2g IV q12h or Cefoxitin 2g IV q6h **+** Doxycycline 100mg PO or IV q12hrs
- 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

Epididymitis

- In young men:
  - C. trachomatis (70%)
  - N. gonorrhoeae (30%)
- In older men: E. coli causes majority of cases
- Therapy:
  - **Ceftriaxone 250mg IM x 1 + 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 x 1 + levofloxacin x 10 days
  - For acute epididymitis most likely caused by enteric organisms: Levofloxacin 500mg PO x 10 days

Thank you

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