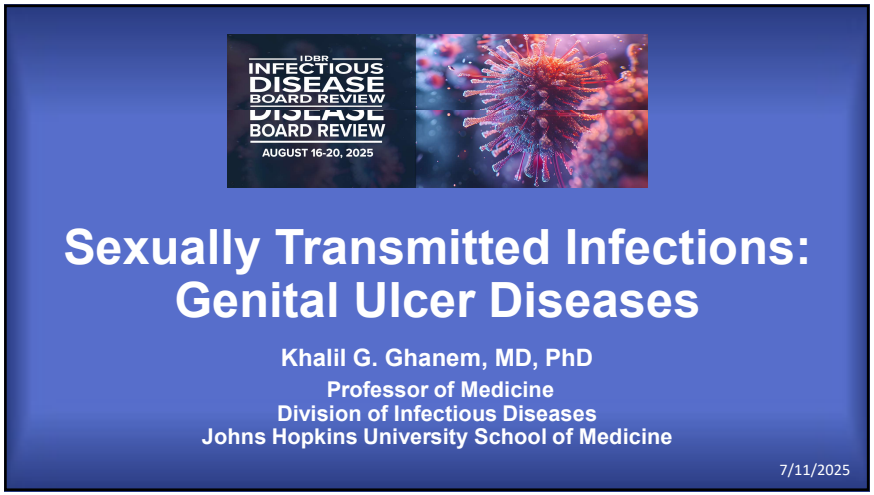
22 Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD, PhD



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Note

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
  - Data on the epidemiology and management of STIs in transgender populations are very limited
- All photos are freely available from the following website unless otherwise noted: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

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Genital Ulcer Diseases (GUD)

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

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Pain and GUD

Which ulcers are PAINFUL?

- HSV
- Chancroid
- Monkeypox

Which ulcers are PAINLESS?

- Syphilis*
- LGV (but lymphadenopathy is PAINFUL)
- Granuloma inguinale

* >30% of patients have multiple painful lesions

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"Keywords" in GUD

- SYPHILIS: Single, **painless** ulcer or chancre at the inoculation site with heaped-up borders & clean base; painless bilateral LAD (>30% of patients have multiple painful lesions)
- HSV: multiple, **painful**, superficial, vesicular or ulcerative lesions with erythematous base

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"Keywords" in GUD (Cont.)

- **CHANCROID**: painful, indurated, 'ragged' genital ulcers & tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- **GI**: **Painless**, progressive (destructive), **"serpiginous"** ulcerative lesions, without regional lymphadenopathy; beefy red with white border & highly vascular
- **LGV**: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy; "groove sign"**

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Question #1

PREVIEW QUESTION

A 35-year-old woman presents with a painless ulcer on her vulva and one on her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms.

Examination reveals the two ulcers with heaped-up borders and a clean base.

Which of the following diagnostic tests is inappropriate to obtain?

A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

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IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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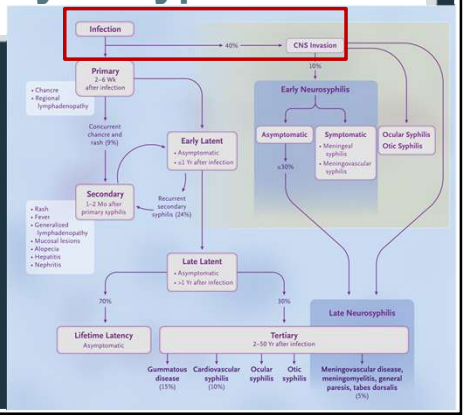
Natural History of Syphilis

Sexual transmission (only occurs in early stages)
- Risk of infection after 1 exposure: 40%
- Index patient is most contagious during 1º and 2º stage, less so in early latent stage

Vertical transmission (may occur during any stage)
- ~80% transmission in the early stages
- ~10% transmission in the late stages

Rarely, transmission may occur through **blood transfusions** and **organ transplantations**



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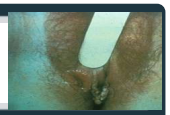
Early Syphilis: Clinical Manifestations



- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 weeks
- Secondary: **Systemic symptoms**: low-grade fever, malaise, sore throat, adenopathy
  - RASHES: [1]evanescent, copper-colored, macular (dry) rash; followed by [2] a red papular eruption (involving palms and soles in 60%); mucosal lesions (gray plaques or ulcers) ; condyloma lata- wart-like lesions that develop in moist areas
  - Other manifestations: Patchy alopecia, hepatitis (mild elevation of aminotransferases with disproportionately high alkaline phosphatase), gastritis, periostitis, glomerulonephritis, etc.

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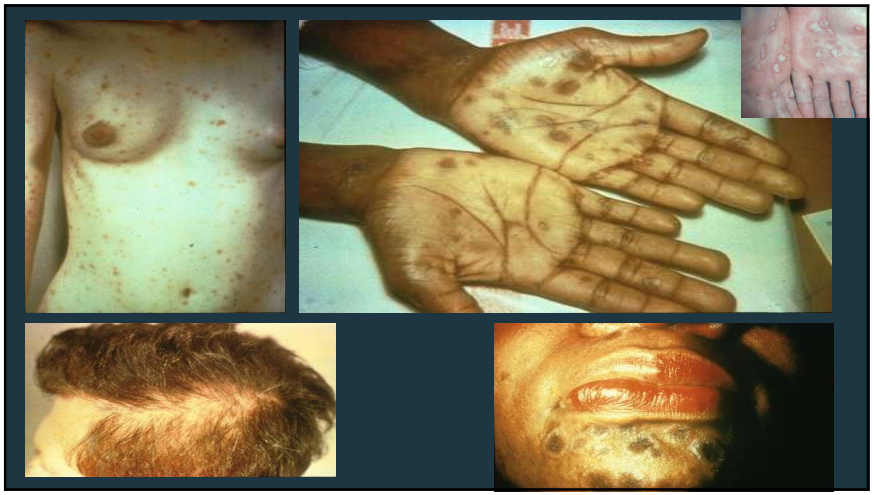

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Neurological Manifestations of Syphilis

- **Can occur during any stage of infection******
- **Symptomatic Early Neurosyphilis**
  - Occurs within the **first year** after infection
  - **Mainly among PWH**
  - **Presents as (basilar) 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
    - Parenchymatous

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Late Neurosyphilis (Tertiary)

Meningovascular

- 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

Parenchymatous

- 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

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Other Tertiary Manifestations

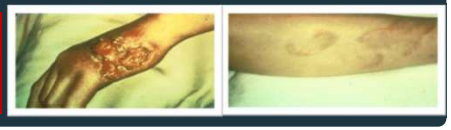
Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

Late benign syphilis

- 'Gummas'
- Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)

~30% of patients with cardiovascular and gummatous syphilis will have asymptomatic neurosyphilis- perform CSF exam!



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Syphilis: Eyes and Ears

Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye; 50% bilateral
  - Uveitis most common
  - Interstitial keratitis: occurs in both congenital (typically at age 5-20; 80% bilateral) and acquired (both early and late infections)
  - **CSF examination normal in ~30% of cases of ocular syphilis**

Ears

- Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, tinnitus or vertigo)
  - Congenital (early and late)
  - Acquired (secondary and late stages)
  - **CSF examination is normal in at least 40% of cases of otic syphilis**

***No need for a CSF examination in patients who only have ocular or otic symptoms/signs

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Syphilis Serological Testing

Nontreponemal tests

- RPR (serum) or VDRL (serum or CSF)
- **False positives:** endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- **False negatives:** PROZONE effect and in early infection
- Reactive result must be confirmed with treponemal test
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (**irrespective of the end-titer**)
- **Titers will decline with or without treatment**

Treponemal tests

- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- **False positives:** Endemic treponemal infections (e.g. yaws, pinta, bejel); Lyme disease; rarely in autoimmune conditions
- **False negatives**: Early primary syphilis
- **Once reactive, always reactive even after appropriate therapy**
  - **Exception: ~25% of persons treated early in primary syphilis may seroorevert years later**

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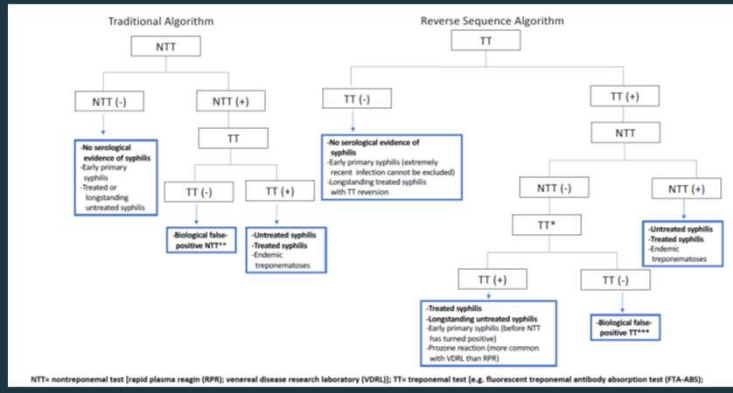

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Syphilis: Diagnostics

- **Darkfield microscopy or PCR 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**
- **Two POC and one at-home tests are now FDA cleared; all detect treponemal antibodies**

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Neurosyphilis: Diagnostics

- No single test can be used to diagnose neurosyphilis
  - CSF pleocytosis **most sensitive** marker
  - 50% of neurosyphilis cases may have negative CSF VDRL; it is **highly specific**, but **insensitive**
  - CSF treponemal tests are very sensitive but NOT specific (i.e. high false+)
    - May be used to **rule out** neurosyphilis
  - ~30% of persons with LATE neurosyphilis may have nonreactive SERUM nontreponemal tests

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A Few Important Concepts to Remember ABOUT Neurosyphilis, Ocular Syphilis, and Otic Syphilis

A normal CSF examination rules out neurosyphilis, but it does not rule out ocular or otic syphilis

A patient with ocular only or otic only signs and/or symptoms does not need a CSF examination. An immediate through clinical evaluation is warranted and if the clinical picture is consistent with ocular or otic syphilis, start antibiotic therapy

A patient with both neurological signs/symptoms and ocular or otic signs/symptoms should undergo a CSF examination. While it may not impact the treatment decision, it may impact diagnostic considerations [patients may have neurological manifestations due to something other than syphilis- you don't want to delay the diagnosis]

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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 X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg PO BID X 4 weeks

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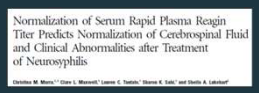
Syphilis Therapy (Cont.)

- Neurosyphilis/Ocular/Otic syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
  - **Follow-up CSF exams are NOT necessary if patient improves clinically, serologically, and is not immunosuppressed (PWH on ART at time of diagnosis do not need a f/u CSF exam)**


Normalization of Serum Rapid Plasma Reagin Titer Predicts Normalization of Cerebrospinal Fluid and Clinical Abnormalities after Treatment of Neurosyphilis


SCIENTIFIC REPORTS
Serological Response Predicts Normalization of Cerebrospinal Fluid Abnormalities at Six Months after Treatment in HIV-Negative Neurosyphilis Patients

- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

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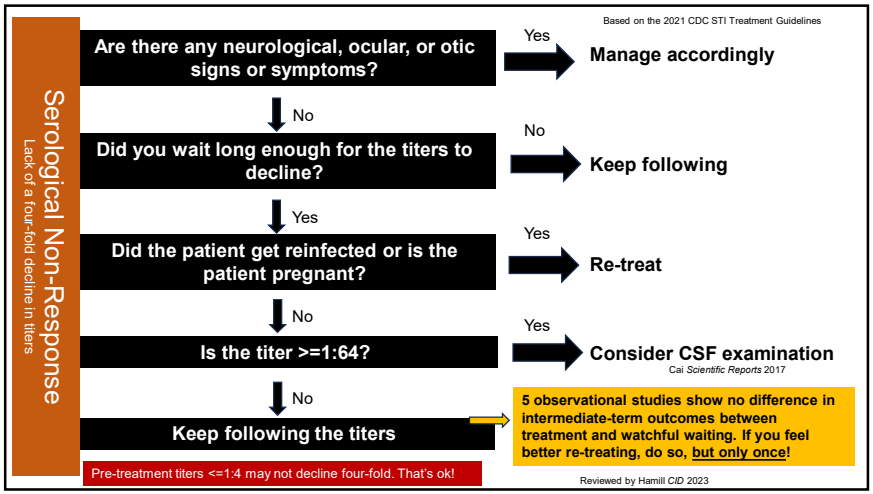

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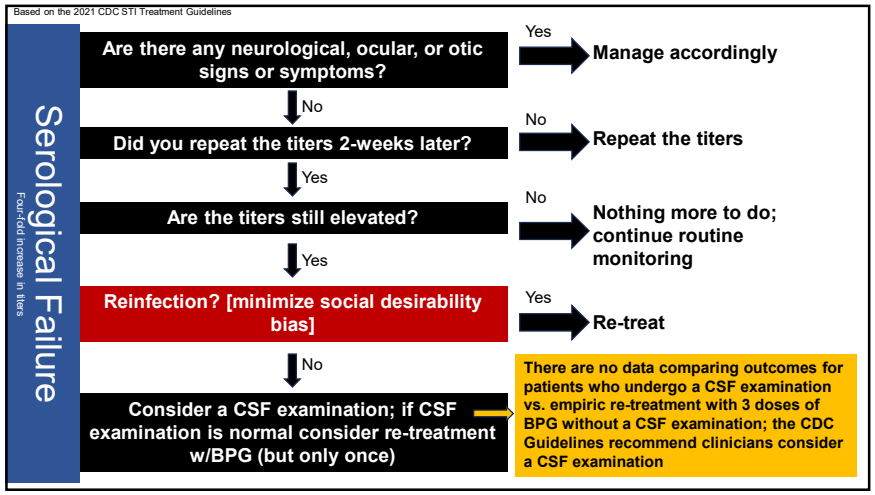

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Question #2

A 37-year-old man presents with a rash, lymphadenopathy, and low-grade fevers. A history of a condomless exposure 3 months earlier prompts the clinician to test for STIs. The following results are obtained: Treponemal EIA reactive; RPR reactive at **1:2048**. The patient is treated with a single IM dose of 2.4 MU of BPG.

- RPR titers 3 and 6 months later are 1:1024
- RPR 12 months after Rx is 1:512

The patient is doing well and denies any re-exposures

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Question #2

Which of the following is the most appropriate intervention at 12 months?

A. BPG 2.4 MU IM X 1
B. BPG 2.4 MU IM X 3
C. Continue to follow
D. CSF examination

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Syphilis & HIV

- Clinical manifestations similar but timeline may be compressed
  - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV negative
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

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Syphilis & Pregnancy

- Screen at 1st prenatal visit, 28 weeks, and at the time of delivery (new ACOG recommendation)
- Screen all those who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic patients with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

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Syphilis Prevention

- Screen
- Treat
- Identify partners and treat partners
- Male condoms
- Doxy PEP (covered in the next STI lecture)

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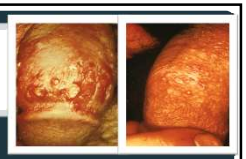
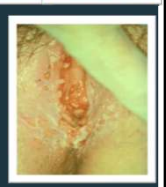
HSV





- Both HSV-1 and HSV-2 cause genital disease
- HSV-1 is now 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
- HSV suppressive therapy in PWH with a history of HSV and who are starting ART- but only if their CD4 <200 cells/mm^3

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HSV Take-home Messages

- 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 those who have active lesions or prodromal symptoms at the time of delivery

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HSV: Diagnostics in Patients with Genital Ulcers

- Tzanck smear (40% sensitive)
- Culture (sensitivity 30-80%)
  - Mainly used for antiviral susceptibility testing
- Antigen detection (~70% sensitive)
- PCR (FDA cleared, >90% sensitive)
  - **Preferred diagnostic test when a lesion is present**

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HSV: Diagnostics in Asymptomatic Patients

- Use Glycoprotein G-based type-specific EIA assays
  - If gG2 is reactive, patient has genital herpes
    - Assay has low specificity depending on EIA index value cutoff; for an EIA cutoff <3, a second confirmatory test that uses a different HSV antigen must be performed (HSV Biokit or HSV Western Blot)
  - If gG1 is reactive, patient either has oral herpes or genital herpes (assay has low sensitivity)
- Serologic testing **NOT** routinely recommended for screening
- **Never obtain IgM or try to interpret IgM results!**

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HSV: Pregnancy

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery is up to 80%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- C-sections are recommended ONLY IF ACTIVE LESIONS OR PRODROMAL SYMPTOMS (i.e. vulvar pain/burning) PRESENT AT DELIVERY
  - ACOG: "For women with a primary or nonprimary first-episode genital HSV infection during the 3rd trimester of pregnancy, cesarean delivery MAY BE OFFERED due to the possibility of prolonged shedding". ACOG Practice Bulletin #220, May 2020
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking.
  - ACOG: Those with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation ACOG Practice Bulletin #220, May 2020 & Cochrane Systematic Review 2008: https://doi.org/10.1002/14651858.CD004946.pub2

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Chlamydia Trachomatis L1-L3: LGV

- Classical 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)

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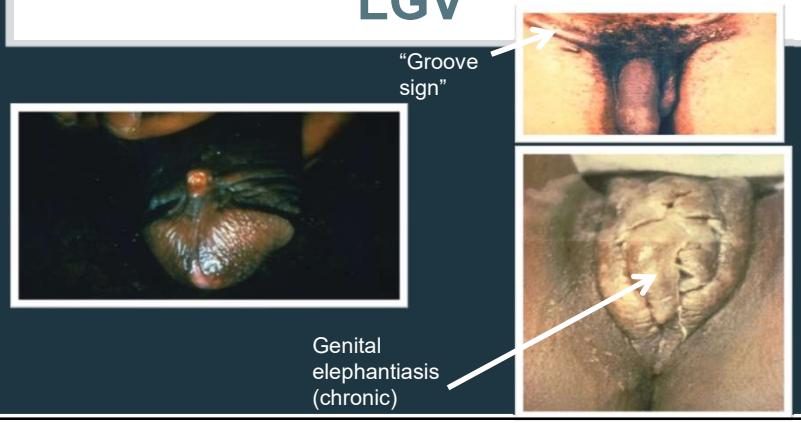
LGV



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LGV Diagnosis & Therapy

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes but is NOT commercially available. Serology is NOT standardized and is NOT recommended
- Therapy: **doxycycline 100mg PO BID X 3* weeks (preferred)** or azithromycin 1g PO q week X 3 weeks (alternate)
- **Patients with *C trachomatis* and a + rectal NAAT:**
  - **Mild symptoms- treat with doxycycline for 1 week**
  - **Moderate to severe symptoms- treat with doxycycline for 3 weeks**

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Chancroid

- *Haemophilus ducreyi*
  - Endemic in parts of the southern US. Rates have gone down
  - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, 'ragged' genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected with syphilis or HSV; bacterial superinfection not uncommon
- Dx: culture (80% sensitive) [antigen detection and PCR not widely available]
- Rx: Azithromycin 1g PO X1 OR Ceftriaxone 250mg IM X1 (erythromycin and ciprofloxacin may also be used)
- Treat all partners in preceding 60 days

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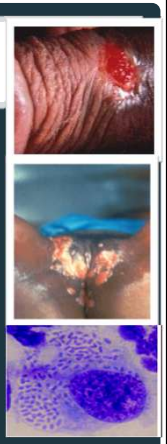
Granuloma Inguinale or Donovanosis

- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with white border & highly vascular
- Dx: tissue biopsy (no culture test; PCR not FDA cleared); demonstrating the organisms in macrophages, called **Donovan bodies**, using **Wright-Giemsa** stain (NOT Gram's stain)
- Rx: Doxycycline 100mg PO BID X 3 weeks (or until resolution) OR azithromycin 1g PO q week X3 (can also use trimethoprim/sulfa)



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MPOX: Epidemiology

- Geographic distribution: Clades 1 (Congo basin) & 2 (West Africa); virulence varies with clade type; clades 1a [children; multiple zoonotic introductions & less efficient person-to-person] and 1b [adults; sexual transmission; more efficient transmission]; 2022-2023 Outbreak: Clade 2b; most cases in men who report sexual contact with other men Transmission via direct contact with sores or bodily fluids (likely most efficient); median duration of PCR detection in lesions is 25 days. Other routes include fomites; respiratory secretions (animal data; limited human data); vertical transmission; percutaneous.
- Transmission most likely to occur when symptoms begin (but risk may begin up to 4 days prior to symptom onset); a person is no longer contagious when all scabs have fallen off & re-epithelialization has occurred.

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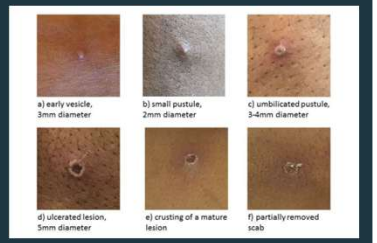
Mpox: Clinical Manifestations

- Incubation: 4 to 21 days
- Prodrome:(up to 70% of patients): Fever, chills, headache, back pain, fatigue
- Rash: (2 days before to 4 days after prodrome); painful; macules to papules to pseudo-pustules; traditionally lesions begin simultaneously and evolve together, but in 2022 outbreak- not all lesions were at the same stage; in 2022 outbreak lesions were mainly anogenital or perioral.
- Other manifestations: proctitis; tonsillitis; ocular (conjunctivitis, blepharitis, keratitis); neurologic (encephalitis) and other less common manifestations



UK Health Security Agency

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Mpox Treatment

- Supportive care
- Antivirals: data supporting efficacy are limited; **none FDA approved for mpox**; tecovirimat (TPOXX) for 2 weeks in patients with or at-risk for severe disease: age < 18; immunocompromised; pregnant; ocular disease (CDC-held Emergency Access Investigational New Drug Protocol); no benefit for tecovirimat in Clade 1 N Engl J Med 2025;392:1484 [cidofovir & brincidofovir unlikely to be on Boards]; trifluridine may be considered for ocular complications

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Mpox Prevention

- Vaccines: Prior vaccinia vaccination appears to provide some protection against severe mpox disease (but not necessarily infection); 2 vaccines available: modified vaccinia Ankara (MVA; JYNNEOS)[attenuated non-replicating vaccinia virus; 2 doses]-preferred; ACAM2000 [replication-competent] associated with more side effects. Vaccinate those with risk factors: (1)Age > 18 years + MSM or (2) if traveling to an area with active spread of clade 1 with anticipated exposure or (3)occupational risks. NO routine vaccination of healthcare workers. **Vaccine may be given as PEP (within 4 days but up to 14 days) following a high-risk exposure** (e.g., sexual or intimate contact). **Monitor those exposed for 21 days**.
- Vaccinia Ig (VIG) in highly immunocompromised persons (don't use with vaccine)
- **Prevention in healthcare settings**: contact+ droplet+ airborne precautions: gowns, gloves, eye protection, and N95 (or equivalent)

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Other Causes Of GUD

- Infectious
  - Mycobacteria (TB)
  - Fungi (candida; blastomycosis)
  - Parasites (leishmania)
- Non-infectious
  - Behcet's
  - Granulomatosis with polyangiitis
  - Fixed drug eruption
  - Psoriasis

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GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
Chancroid (H. ducreyi)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (C. trachomatis)	Painless	short-lived ulcer, painful suppurative LAD, "groove sign" PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline (preferred) -Azithromycin (alternate)
Granuloma Inguinale (Klebsiella granulomatis)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim

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THANK YOU!

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