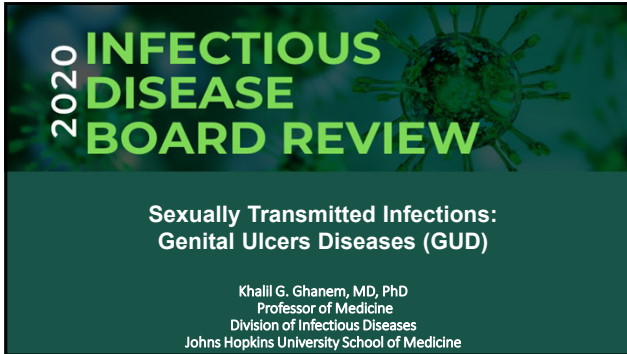


15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

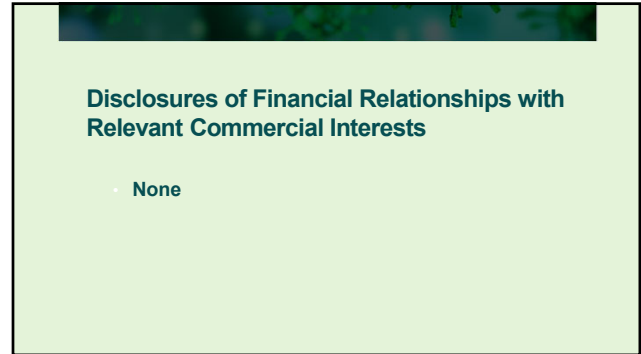
Speaker: Khalil Ghanem, MD



2020 **INFECTIOUS DISEASE BOARD REVIEW**

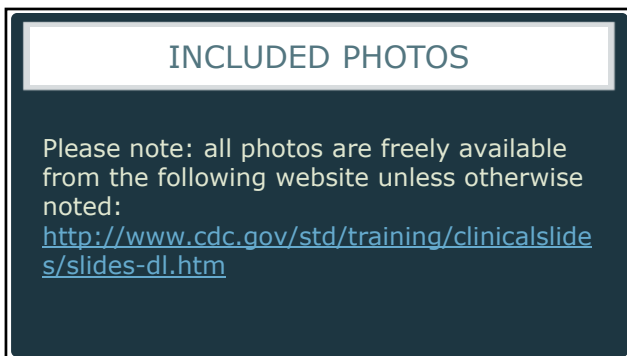
Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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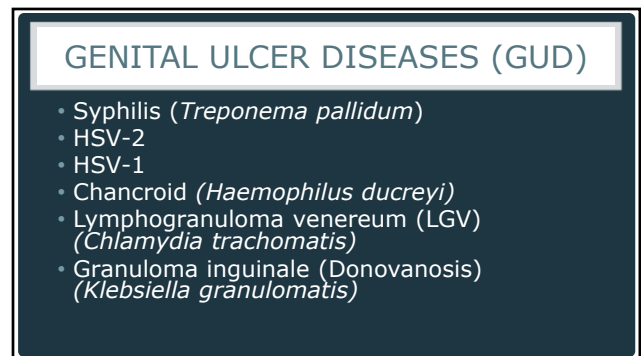
Disclosures of Financial Relationships with Relevant Commercial Interests

- None



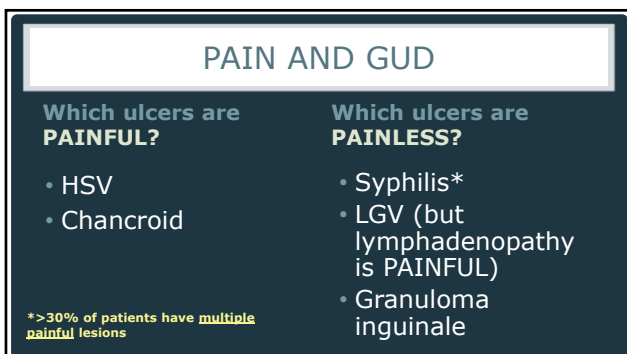
INCLUDED PHOTOS

Please note: all photos are freely available from the following website unless otherwise noted:
<http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm>



GENITAL ULCER DISEASES (GUD)

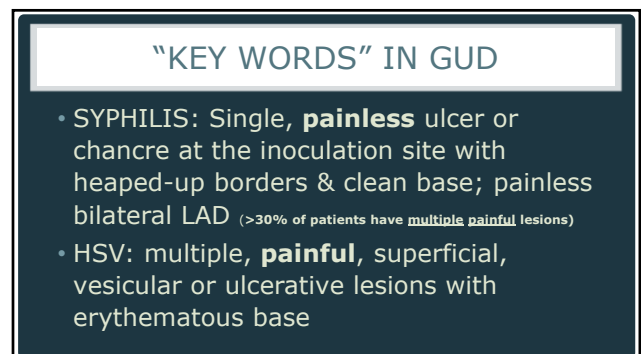
- Syphilis (*Treponema pallidum*)
- HSV-2
- HSV-1
- Chancroid (*Haemophilus ducreyi*)
- Lymphogranuloma venereum (LGV) (*Chlamydia trachomatis*)
- Granuloma inguinale (Donovanosis) (*Klebsiella granulomatis*)



PAIN AND GUD

Which ulcers are PAINFUL?	Which ulcers are PAINLESS?
<ul style="list-style-type: none">• HSV• Chancroid	<ul style="list-style-type: none">• Syphilis*• LGV (but lymphadenopathy is PAINFUL)• Granuloma inguinale

* >30% of patients have **multiple painful lesions**



“KEY WORDS” 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

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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"KEY WORDS" IN GUD CONTINUED

- 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**"

GUD: CONCEPTS TO KNOW

- Organisms that cause disease
- Geographic distribution for less common agents
- Diagnostic approach(es)
- Therapeutic approach(es)

QUESTION #1

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.

QUESTION #1

Which of the following diagnostic tests is **inappropriate** to obtain?

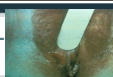
- A. Serum RPR
- B. Serum VDRL
- C. Serum treponemal EIA
- D. Darkfield microscopy on a specimen obtained from the oral ulcer
- E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

SYPHILIS: TAKE-HOME POINTS

- Neurological and ocular manifestations may occur during any stage of syphilis
- Both treponemal and non-treponemal tests may be nonreactive in primary syphilis but they are almost ALWAYS reactive in secondary and early latent syphilis (remember prozone reaction for non-treponemal test in secondary syphilis)
- Treponemal tests are almost always reactive in late syphilis (once positive always positive) irrespective

EARLY SYPHILIS: CLINICAL MANIFESTATIONS

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



15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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NEUROLOGICAL MANIFESTATIONS OF SYPHILIS

- Can occur during any stage of infection
- Can be either 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
 - Parenchymatous

LATE NEUROSYPHILIS (TERTIARY)

<h4>Meningovascular</h4> <ul style="list-style-type: none"> • 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 	<h4>Parenchymatous</h4> <ul style="list-style-type: none"> • 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

<h4>Cardiovascular</h4> <ul style="list-style-type: none"> • 15-30 years after latency • Men 3X> women • Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis 	<h4>Late benign syphilis</h4> <ul style="list-style-type: none"> • 'Gummas' • Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)
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SYPHILIS: EYES AND EARS

<h4>Eyes</h4> <ul style="list-style-type: none"> • Ocular manifestation may occur during any stage and may involve any portion of the eye <ul style="list-style-type: none"> • Uveitis & neuroretinitis: mainly secondary stage • 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 	<h4>Ears</h4> <ul style="list-style-type: none"> • Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, ringing or vertigo) <ul style="list-style-type: none"> • Congenital (early and late) • Acquired (secondary and late stages) • CSF examination is normal in >90% of cases of otic syphilis
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SYPHILIS SEROLOGICAL TESTING

<h4>Nontreponemal tests</h4> <ul style="list-style-type: none"> • RPR (serum) or VDRL (serum or CSF) • May be used as screening test (traditional algorithm) • False+: endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections • Reactive result must be confirmed with treponemal test • False negative: PROZONE effect • Four-fold (i.e. 2-dilution) decline after treatment = CURE (irrespective of the end-titer) 	<h4>Treponemal tests</h4> <ul style="list-style-type: none"> • 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
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15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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SEROLOGICAL TESTING: DIFFERENT ALGORITHM

- | | |
|--|--|
| +EIA/ -RPR / -FTA Abs | +EIA/ -RPR / +FTA Abs |
| <ul style="list-style-type: none">False positive EIA<ul style="list-style-type: none">See previous slide | <ul style="list-style-type: none">The patient had syphilis in the past and was adequately treatedThe patient had syphilis in the past but was not adequately treatedThe patient has early syphilis and the EIA became positive before the RPR did (this is rare)Prozone reaction in secondary syphilis |

SYPHILIS: DIAGNOSTICS

- 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*



SYPHILIS: DIAGNOSTICS CONTINUED

- No single test can be used to diagnose neurosyphilis
 - 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 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 X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks

SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular syphilis
 - Aqueous penicillin 18 to 24 MU IV X 10-14 days
 - Procaine penicillin 2.4 MU IM qd + probenecid 500 mg po QID X 10-14 days
 - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **may induce early labor**

QUESTION #2

A pregnant HIV+ woman (CD4 260 cells/mm³; HIV RNA <50 copies/ml) on ART presents with a diffuse rash.

On examination, she has a temperature of 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.

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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QUESTION #2

Which of the following antibiotics is most appropriate?

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

SYPHILIS & HIV

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

SYPHILIS & PREGNANCY

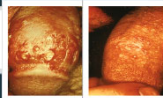
- Screen all women at 1st prenatal visit
- Screen all high risk women and those women living in high-prevalence areas twice in the 3rd trimester: at 28-32 weeks and again at the time of delivery
- Screen all women who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic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

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 women who have active lesions at the time of delivery

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%)**
- Antigen detection (~70% sensitive)
- **PCR (FDA cleared, >90% sensitive)**

Asymptomatic Patient

- Use **Glycoprotein G-based type-specific assays** (gG1 & gG2)
- If gG2 is reactive, patient has genital herpes*
- If gG1 is reactive, patient either has oral herpes or genital herpes**
- **Positive predictive value is low in low prevalence settings**
- Serologic testing NOT routinely recommended for screening
- **Never** obtain IgM or try to interpret IgM results!
- * Assay has low specificity depending on cutoff
- ** Assay has low sensitivity

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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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= 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 PRODRROMAL 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: Women 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>*

QUESTION #3

A 32 year-old man presents with a single, non-painful, clean-based penile ulcer that developed 3 days earlier

He was in India for 2 weeks 5 months ago

His physical examination is otherwise unremarkable

Serum RPR is negative

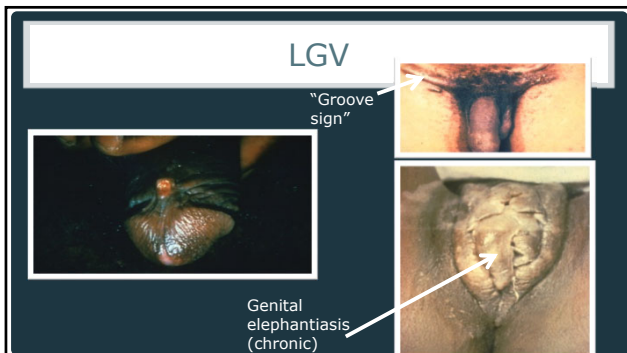
QUESTION #3

What is the **most appropriate next step**?

- A. Obtain a tissue biopsy to evaluate for *Klebsiella granulomatis*
- B. Obtain a serum FTA-Abs
- C. Perform darkfield microscopy on a swab from the ulcer
- D. No further testing; treat with doxycycline for two weeks
- E. Serum glycoprotein G-based testing

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)



LGV DIAGNOSIS & THERAPY

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes. Serology may support the clinical diagnosis but is not a definitive diagnostic test; four-fold rise of IgM and IgG antibody is diagnostic of active infection. A single IgM antibody >1:64 or single IgG >1:256 are considered positive for invasive disease (standardized for genital infections).
- Therapy: **doxycycline 100mg PO BID X 3* weeks** or **azithromycin 1g PO q week X 3 weeks**

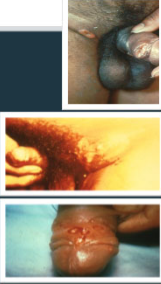
*Experts feel that in mild LGV proctitis, 1 week of doxycycline or 2g of azithromycin is sufficient

15 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

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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



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, and ciprofloxacin) +/- aminoglycoside if slow to improve



GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet -Cidofovir
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin -Doxycycline
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 -Azithromycin
Granuloma Inguinale (Klebsiella granulomatis)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim -Ciprofloxacin -Aminoglycosides