# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*


**Sexually Transmitted Infections: Genital Ulcer Diseases**

**Khalil G. Ghanem, MD, PhD**
**Professor of Medicine**
**Division of Infectious Diseases**
**Johns Hopkins University School of Medicine**

**7/18/2024**


- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  **- None**

## 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

## 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

## 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**

## "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

# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*

## "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"**

## 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?

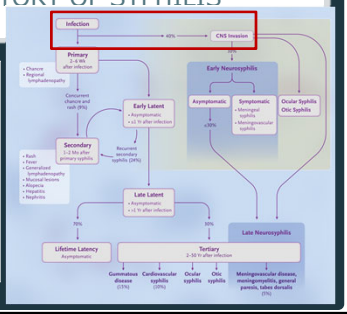
A. Serum RPR
B. Serum VDRL
C. Serum treponemal EIA
D. Darkfield microscopy on a specimen obtained from the oral ulcer
E. Darkfield microscopy on a specimen obtained from the vulvar ulcer

## NATURAL HISTORY OF SYPHILIS

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

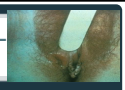
**Vertical transmission** (may occur during any stage)
- ~80% transmission in the early stages
- ~10% transmission in the late stages

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

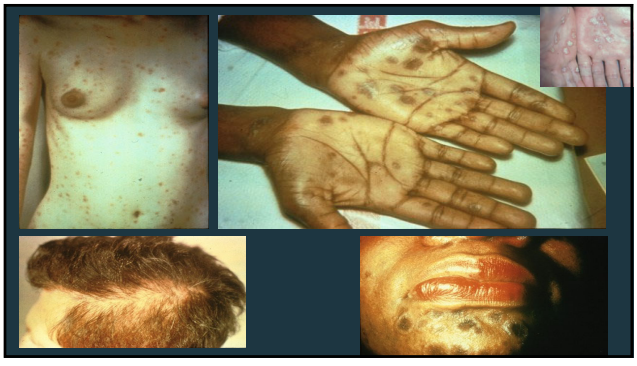



N Engl J Med 2020;382:845-854

## 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.



# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*

## 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 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)

### 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

## OTHER TERTIARY MANIFESTATIONS

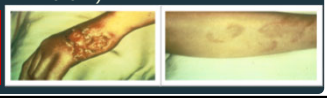
### Cardiovascular

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

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

### Late benign syphilis

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



## SYPHILIS: EYES AND EARS

### Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye
  - 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**

### 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**

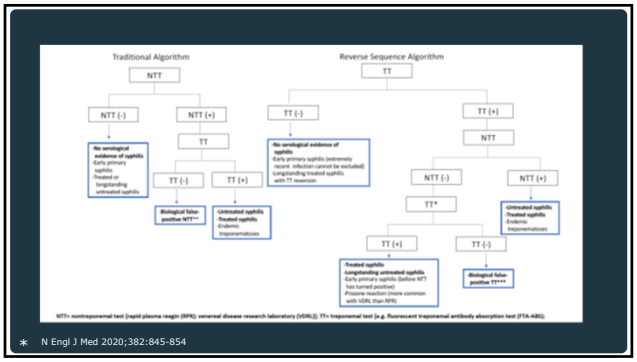
## SYPHILIS SEROLOGICAL TESTING

### 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 serorevert years later**




* N Engl J Med 2020;382:845-854

# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*

## 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

## 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

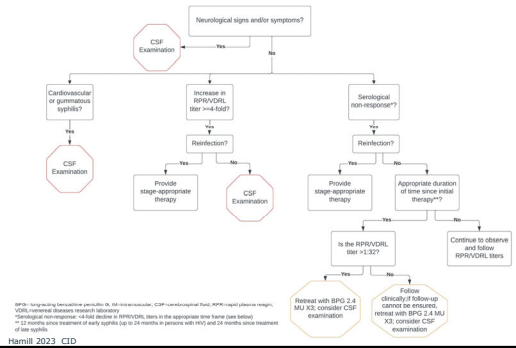
## A FEW IMPORTANT CONCEPTS TO REMEMBER ABOUT NEUROSYPHILIS, OCULAR SYPHILIS, AND OTIC SYPHILIS

**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]**

## Who Should Have a CSF Exam?




Hamill 2023 CID

## 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

## Serological Non-Response

**Are there any neurological, ocular, or otic signs or symptoms?** Yes → **Manage accordingly**

No ↓

**Did you wait long enough for the titers to decline?** No → **Keep following**

Yes ↓

**Did the patient get reinfected or is the patient pregnant?** Yes → **Re-treat**

No ↓

**Is the titer >=1:64?** Yes → **Consider CSF examination**

Cai *Scientific Reports* 2017

No ↓

**Keep following the titers**

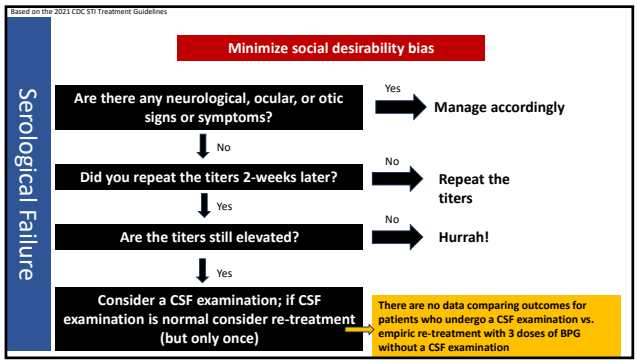
**5 observational studies show no difference in intermediate-term outcomes between treatment and watchful waiting. If you feel better re-treating, do so, but only once!**

Based on the 2021 CDC STI Treatment Guidelines

Reviewed by Hamill *CID* 2023

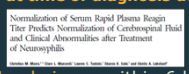
# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*




## SYPHILIS THERAPY CONTINUED

- 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 does 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

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

## QUESTION #2

PREVIEW QUESTION

A pregnant patient with HIV(CD4 260 cells/mm$^3$; 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.

## QUESTION #2

PREVIEW QUESTION

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
  - 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)

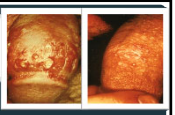
## SYPHILIS & PREGNANCY

- Screen at 1st prenatal visit
- Screen higher risk patients and those living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- 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)**

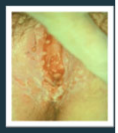
# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

*Speaker: Khalil Ghanem, MD*

## 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$^3$



## 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

## 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**

## 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!**

## 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

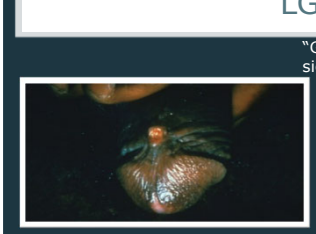
## CHLAMYDIA TRACHOMATIS L1-L3: LGV

- 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)

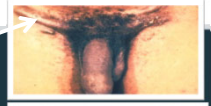
# 23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

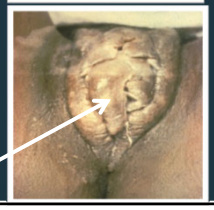
*Speaker: Khalil Ghanem, MD*

## LGV



"Groove sign"





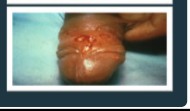
Genital elephantiasis (chronic)

## 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**

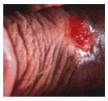
## CHANCROID

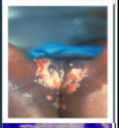
- *Haemophilus ducreyi*
  - Endemic in parts of the southern US. Rates have gone down
  - Increased risk with HIV infection and commercial sex work
- Symptoms: painful, indurated, 'ragged' genital ulcers & tender suppurative inguinal adenopathy (50%); kissing lesions on thigh; 10% of patients co-infected 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

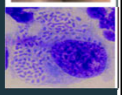


## GRANULOMA INGUINALE OR DONOVANOSIS

- *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)

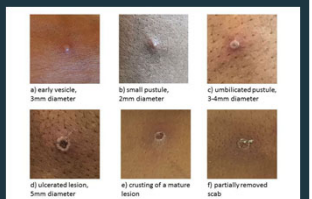






## MONKEYPOX

- Prodrome: Fever, chills, rash, or new lymphadenopathy; however, onset of perianal or genital lesions (often painful) in the absence of prodrome may occur; proctitis described
- DDx rash: Secondary syphilis, HSV, chancroid, and VZV. Consider in men who report sexual contact with other men (incubation 5-21 d) & individuals reporting a significant travel history
- Patients generally describe close, sustained physical contact with other people with monkeypox (respiratory transmission inefficient)
- Persons are infectious once symptoms begin; when all scabs have fallen off a person is no longer contagious
- Rx: Tecovirimat in patients with or at-risk for severe disease (CDC-held Emergency Access Investigational New Drug Protocol )




UK Health Security Agency

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

**23 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)**

*Speaker: Khalil Ghanem, MD*