

New Guidelines for Treating STDs

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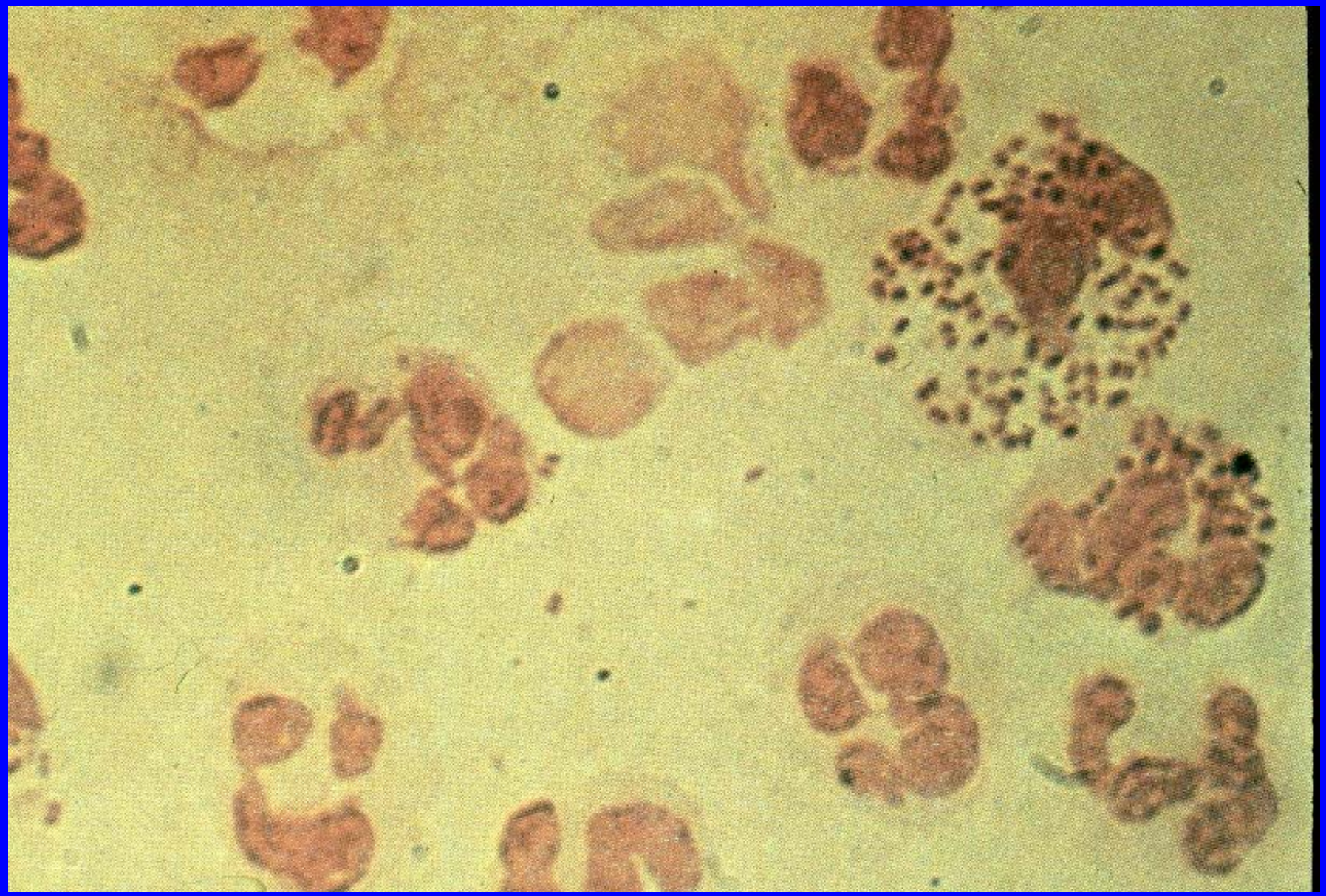
Pre-Exposure Vaccination

- Hepatitis B

- Sexual transmission accounts for 30-60% of 240,000 new HBV infections annually in the U.S.
- Vaccine: 3 doses at 0, 1-2, 4-6 months
 - . Protective antibody levels: 50% after 1 dose, 85% after 2 doses, >90% after 3 doses
 - . If series interrupted, give missing dose ASAP: no need to re-start series (give in deltoid, not buttocks)
- Sexual contact with person with acute HBV infection:
 - . Give HBIG and start vaccine series within 14 days - prevents 75% of infections

Pre-Exposure Vaccination

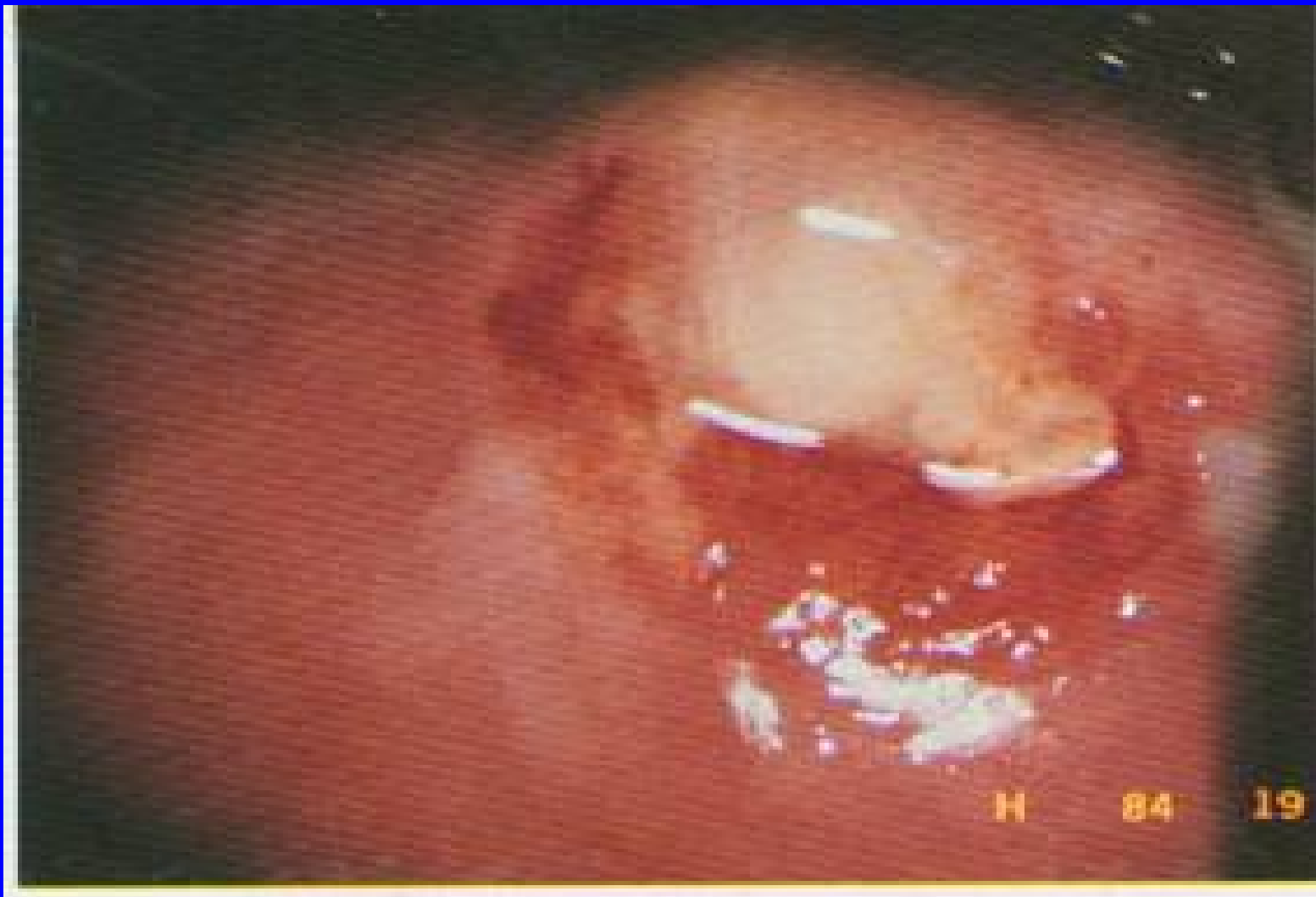
- Hepatitis A
 - Self-limited infection, no chronic disease, but can cause serious acute infection
 - . Most reported source: household or sexual contact
 - 33% of U.S. population has serologic evidence of exposure
 - Hepatitis A vaccine: 2-dose series, 97-100% effective at producing immunity
 - Post-exposure: single IM dose of IG and start vaccine series..... As of 6/07, HAV vaccine alone if < 40



Gonorrhoea in Women

- **Up to 80% asymptomatic in screening populations**
- **Variable incubation period (most symptomatic within 10 days)**
- **Mucopurulent cervicitis**

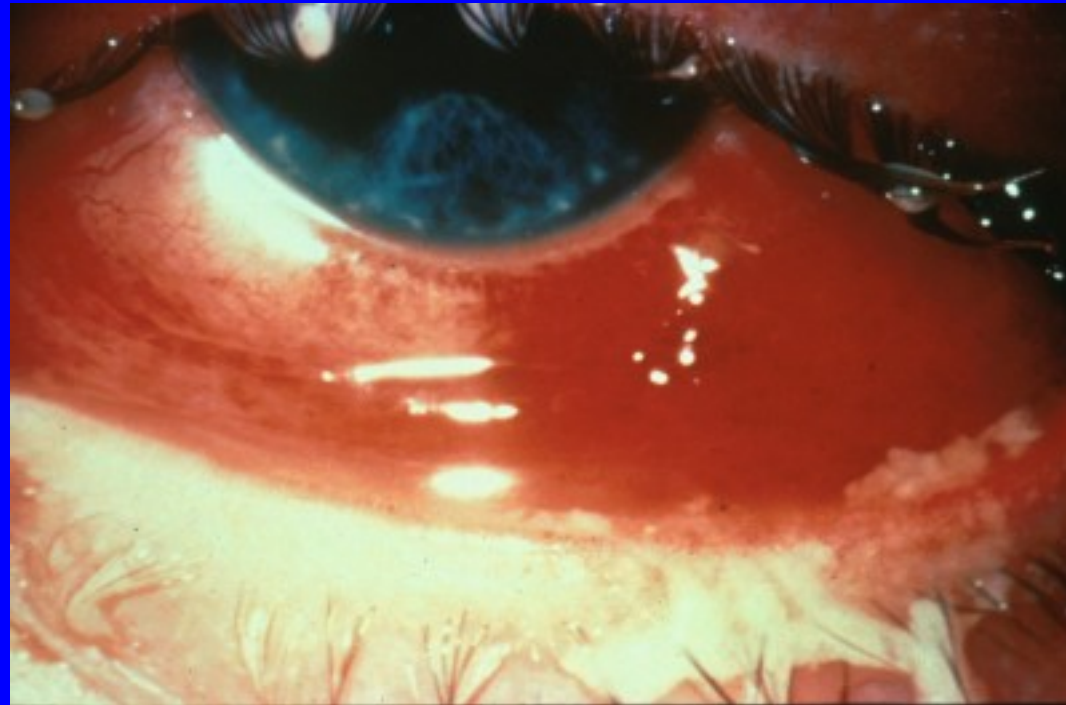
Gonococcal Cervicitis



Gonorrhea in Women: Other Sites

- **Anorectal co-infection in 40%**
- **Pharyngeal co-infection in 15%**
 - **Rates of both higher in pregnancy**
- **Ocular infection**
- **Salpingitis/PID in 10-20%**

Gonococcal ophthalmia



Gonorrhoea: Transmission Rates

- **Female-to-male: 20% per episode of vaginal intercourse**
 - **60-80% infection with ≥ 4 exposures**
- **Male-to-female: 50% risk per contact**
 - **$\geq 90\%$ rate after 2-3 exposures**
- **40% of asymptomatic male contacts of infected women will also have positive cultures**

Gonococcal Infections: Uncomplicated Cervix, Urethra, Rectum (pre-2006)

Ceftriaxone 125 mg IM x 1

(Cefixime 400 mg po x 1 -- PRODUCTION DC'D IN U.S.)

Ciprofloxacin 500 mg po x 1

Ofloxacin 400 mg po x 1

PLUS Chlamydia treatment

Ceftriaxone/cipro: >99% cure

Cefixime: 97% cure

Spectinomycin 2 gm IM x 1 (98% cure)

Azithromycin 1 gm - only 93% cure

2 gm - expensive/poorly tolerated

Nonavailability of Cefixime

- Recent discontinuation of cefixime (Suprax[®]) production in the U.S. has prompted further examination of alternative oral treatment options for GC
- To be considered as a recommended treatment, a regimen should cure > 95% of urogenital infections
- Available data do not demonstrate any single-dose oral rx other than cefixime or quinolones to meet criteria
 - Cefpodoxime (Vantin): 96% (94-98%) genital cure, 79% pharyngeal
 - Cefuroxime (Ceftin): 96% (95-98%) genital cure; 57% pharyngeal
 - Ceftibuten (Cedax) 98% genital cure, only trial in men with urethritis
 - Cefdinir (Omnicef) ; might be effective, but no published data

MMWR, Nov 22, 2002

Quinolone-Resistant Gonorrhoea (2004/5)

- **QRNG has become common in parts of Asia and the Pacific**
 - **Relatively rare in the continental U.S.**
- **CDC'S Gonococcal Isolate Surveillance Project showed, overall, <0.4% of over 5000 isolates resistant to ciprofloxacin**
- **Resistant organisms made up 0.2% of isolates from 25 GISP cities in continental U.S., but 14.3% of isolates from Honolulu**
- **Quinolones should **not** be used to treat GC in Hawaii or that may have been acquired in Asia/Pacific (including Hawaii)**

CDC, 2007--Quinolones OUT to Treat GC

Ongoing data from CDC 's Gonococcal Isolate Surveillance Project (GISP), including preliminary findings from 2006, demonstrate that fluoroquinolone-resistant gonorrhea is continuing to spread and is now widespread in the United States. As a consequence, and as reported in the MMWR, April 13, 2007, this class of antibiotics is no longer recommended for the treatment of gonorrhea in the United States. Treatment recommendations have been updated accordingly, and are provided below. (*MMWR, 8/07*)

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum*

Recommended Regimens

Ceftriaxone 125 mg IM in a single dose **OR**

Cefixime†400 mg orally in a single dose or 400 mg by suspension (200 mg/5ml)
PLUS TREATMENT FOR CHLAMYDIA IF CHLAMYDIAL INFECTION

* These regimens are recommended for all adult and adolescent patients, regardless of travel history or sexual behavior.

† The tablet formulation of cefixime is currently not available in the United States

Alternative Regimens

Spectinomycin† 2 g in a single intramuscular (IM) dose **OR**

Single-dose cephalosporin regimens † *Spectinomycin is currently not available in the U.S.*

Other single-dose cephalosporin therapies that are considered alternative treatment regimens for uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime 500 mg IM; or cefoxitin 2 g IM, administered with probenecid 1 g orally; or cefotaxime 500 mg IM. Some evidence indicates that cefpodoxime 400 mg and cefuroxime axetil 1 g might be oral alternatives.

Uncomplicated GC Infection of Urethra, Cervix, Rectum: Alternatives?

- **Spectinomycin:**
 - Nonavailability a concern: updates posted on CDC website – esp good for pregnancy but not pharyngeal infx
- **Cephalosporins**
 - Standard is ceftriaxone, with 98.8% (97.7-99.8%) cure rate
 - 400 mg of cefixime has 98% cure, but bactericidal levels not as high or sustained as ceftriaxone
 - Others may be reasonable, but have to accept lower 95% CI cure rate (<90%)
 - Others have been tested in small populations
- **Azithromycin**
 - Single 2-gm dose effective (efficacy 99.2%; CI 97.2-99.9%), but that dose is associated with GI sx in 35% of treated and is expensive
 - Also produces sustained low levels of drug, which can favor resistance
 - 1 gm po better tolerated, but lower efficacy and possible more rapid resistance

Newman LM, et al, CID 4/07, after MMWR 8/06

Treatment of Pharyngeal Gonorrhoea

- More difficult to eradicate than urogenital/rectal
- Treatment for GC and chlamydia recommended
 - **Ceftriaxone 125 mg IM x 1--only option**

N.B.: Spectinomycin not effective in this setting

Disseminated gonorrhoea - skin lesion



Disseminated gonorrhoea - skin lesion



Disseminated GC Infection

- A cephalosporin-based intravenous regimen is recommended for the initial treatment of DGI. This is particularly important when gonorrhea is detected at mucosal sites by nonculture tests.

Recommended Regimen

Ceftriaxone 1 g IM or IV every 24 hours

Alternative Regimens

Cefotaxime 1 g IV every 8 hours OR

Ceftizoxime 1 g IV every 8 hours OR

Spectinomycin† 2 g IM every 12 hour

- Treatment should be continued for 24–48 hours after clinical improvement, at which time therapy may be switched to one of the following regimens to complete at least 1 week of antimicrobial therapy.

DGI: Maintenance Therapy

- **Cefixime † 400 mg orally twice daily**

OR

**Cefixime 400 mg by suspension (200 mg/5ml)
twice daily**

OR

Cefpodoxime 400 mg orally twice daily

† The tablet formulation of cefixime is currently not available in the United States

Chlamydia - Epidemiology

- **Higher prevalence of infection than GC**
- **Asymptomatic infection common in men and women**
- **Isolated from 30-60% of women with GC**
- **Neonatal disease in as many as 2-5% of newborns in high-prevalence areas**

Chlamydia - Testing

- Who to test?

- CDC guidelines: all pregnant women in 1st trimester and patients at high risk rescreened in 3rd trimester

- Recent study: positive test in 1st trimester and treated, risk of positive test in 3rd trimester was 32% (6% risk if initial test was negative). Higher risk associated with age <25 and unmarried

Allaire et al; Inf Dis ObGyn 1998; 6:118

- **DNA amplification tests more sensitive and specific than culture or antigen-detection assays**

- PCR and LCR identify 30% more cases of genital tract infection: can detect small numbers of organisms, esp. in asymptomatic

- LCR: advantage is emerging availability of testing on urine samples

- noninvasive screening test

Bass C, Silverman, et al. J Clin Micro 1993

Weisenfeld HC, Heine RP, et al. AJOG 1996

Chlamydia in Pregnancy

- **Risks of neonatal disease**
 - Conjunctivitis: 18-50%
 - Nasopharyngeal infection: 15-20%
 - Pneumonitis: 3-18%
- **Treatment during pregnancy reduced risk of neonatal infection from 50% to 7% (erythromycin)** *Schachter et al. NEJM 1986; 314:276*
- **Erythromycin has poor compliance due to side effects: recent randomized trials for alternatives**
 - Amoxicillin vs erythromycin
Alany M et al. Lancet 1994; Silverman N et al. AJOG 1994; Magat AH et al. ObGyn 1993
 - Azithromycin vs erythromycin
Rosen M, Silverman N. Inf Dis ObGyn 1997
- **Meta-analysis of amoxicillin vs erythromycin: Amoxicillin more effective and better tolerated** *[Turrentine MA, Newton ER. ObGyn 1995; 86:1021]*

Chlamydia Treatment - Considerations

- Clinical trials show efficacy of azithromycin and doxycycline to be equivalent but in populations with good compliance and follow-up
- In populations with “erratic” compliance, azithromycin may be more cost-effective
 - Ideally, dispensed on-site
- Test of cure: *no earlier than* 3 weeks after completing therapy (false + with dead organisms)
-

Chlamydia Treatment: Adolescents and Adults

- *Treat presumptively in all patients with GC*

Recommended regimens

- ___ - Azithromycin, 1 gm po x 1
- Doxycycline, 100 mg po BID x 7 days

Alternative regimens

- Erythromycin base 500 mg po QID x 7 d
- Ofloxacin 300 mg po BID x 7 day

Pregnancy

- Amoxicillin 500 mg po TID x 7 days
- OR
- Azithromycin 1 gm po x 1

N.B. All erythromycin-based therapies are now *alternatives* in pregnancy

Pelvic Inflammatory Disease

- Upper genital tract infection in women
- Ascending spread of organisms from cervix/vagina to endometrium, tubes, contiguous structures
- May include combination of:
 - Endometritis
 - Salpingitis
 - Tubo-ovarian abscess (TOA)
 - Pelvic peritonitis
- Over 25% of women with PID have at least one sequela
 - Infertility, ectopic pregnancy, chronic pelvic pain

PID and Adolescents

- 70% of patients with PID are < 25, and 33% have first infection at < 20
- Adolescents aged 15-19 have highest rate of PID (adjusted for only sexually active individuals)
- Incidence in sexually active females:
 - 15-year-olds: 1 in 8
 - 16-year-olds: 1 in 10
 - 24-year-olds: 1 in 80
- In sexually active teens:
 - CT (+): 8-25 % GC (+): 3-18 %
 - 80% of GC in 15-to-29-year-olds
- Acute PID develops in 15-40% of CT (+) and 9-15% of NG (+) women who are untreated

Wenstrom L, AJOG 1980

Howell MR, Sex Trans Dis 1997

PID -- Etiology

- **Considered to be a polymicrobial infection**
- **Sexually transmitted organism (CT/NG) isolated (usually from cervix) in 45-65% of PID cases**
- **Anaerobic/facultative bacteria the only organisms recovered in 25-50% of cases**
- **Bacterial vaginosis strongly associated with PID -- shift in normal vaginal flora**
 - ? Primary initiators or secondary invaders
 - May alter natural “barrier” of endocervical canal and cervical mucus to allow easier access to upper tract
 - Douching strongly associated with BV

PID -- Pathogenesis (1)

- **Pathogenic organisms gain access to upper genital tract along endometrial mucosal surface**
- **Natural barriers can be altered: changes in cervical mucus/endogenous immune factors at ovulation and menses**
- **Bacteria may “hitchhike” on sperm and be delivered to upper genital tract**

PID -- Pathogenesis (2)

- **Cervical colonization and retrograde menstruation**
 - PID symptoms usually present within 7 days of menses (up to 75% of cases)
- **GC damages ciliated epithelial cells and produces complement-mediated inflammatory response → scarring and adhesions**
- **CT mediates damage through cell-mediated immune mechanisms that outlast primary chlamydial tubal infection (which tends to be self-limited, less symptomatic)**
 - Perpetuated autoimmune response to CT's heat shock-like protein

PID -- Risk Factors

- **Younger age**
 - Sexual activity/lower access to care
 - Larger zones of cervical ectopy and greater penetrability of cervical mucus
 - Less-cornified vaginal epithelium: more susceptible to infection
- **Menstrual cycle influences**
- **Contraception methods**
- **Older male partners in adolescents**
 - More likely to harbor larger reservoir of asymptomatic infections

PID -- Diagnostic Criteria (*MMWR 2006*)

Minimum criteria (empiric rx in sexually active women)

- Lower abdominal tenderness
- Adnexal tenderness
- Cervical motion tenderness

In patients with any pelvic tenderness and signs of lower genital tract infection, dx of PID should be considered

- In a “see-and treat setting”, WBCs on wet prep associated with markedly elevated risk (RR = 59) of CT or GC ([Hakakha/Silverman, Obstet Gynecol 2002](#))

Additional criteria (supportive of a PID dx)

- Oral temp > 101 F (38.3 C)
- Cervical/vaginal mucopurulent discharge
- WBCs on vaginal wet prep
- Elevated ESR or CRP
- Cervical infection with CT/GC

PID -- Treatment

- Coverage should include NG, CT, anaerobes, facultative gram (-), strep
- Treatment should be initiated as soon as presumptive diagnosis has been made
 - Delay in rx for 3 or more days gives 3X higher likelihood of impaired fertility/ectopic (22% vs 8%)
 - Impact of delay most pronounced for women with CT infection, with 6X ↑ in sequelae (Hillis SD, AJOG 1993)
- PEACH Trial: among women with mild-to-moderate PID, no difference in reproductive outcomes between women randomized to inpt vs outpt treatment arms (Ness RB, AJOG 2002)

PID -- Hospitalize for:

- **Surgical emergencies (e.g. appendicitis) cannot be excluded**
- **Patient is pregnant**
- **No response to outpatient therapy**
- **Patient unable to follow or tolerate outpatient regimen**
- **Severe illness, nausea/vomiting, high fever**
- **Patient has TOA**

MMWR 8/4/06 (RR-11)

PID --Inpatient Treatment Options

Cefotetan 2 g IV Q 12h

OR

Cefoxitin 2 g IV Q 6h

PLUS

Doxycycline 100 mg

PO/IV Q 12

Clindamycin 900 mg IV Q 8h

PLUS

Gentamicin 2 mg/kg loading

dose then 1.5 mg/kg Q 8h

**(single-daily dosing is also
acceptable)**

Stop parenteral therapy 24 hours after pt improving clinically, then:

Doxycycline 100 mg PO BID or Clindamycin 450 mg PO QID

to complete 14 days of therapy

PID -- Outpatient Therapy

Ofloxacin* 400 mg PO

BID X 14d

OR

Levofloxacin* 500 mg PO QD

X 14 d

WITH/WITHOUT

Metronidazole 500 mg PO BID

X 14 d

***If GC testing done and (-)**

Ceftriaxone 250 mg IM X 1

OR

Cefoxitin 2 gm IM X 1 with

Probenecid 1 gm PO X 1

PLUS

Doxycycline 100 mg PO BID

X 14 d

WITH/WITHOUT

Metronidazole 500 mg PO

BID X 14 d

•Followup exam in 72 hours: if no clinical improvement, hospitalize for IV therapy

MMWR 8/4/06

Genital Ulcer Diseases

- **In the U.S., most patients with genital ulcers have:**
 - **Genital herpes (HSV)**
 - **Syphilis**
 - **Chancroid**
- **Less common in U.S. :**
 - **Granuloma inguinale, LGV**
- **Relative frequency of agents varies geographically, but HSV most common**
- **All genital ulcer diseases increase risk for HIV infection**

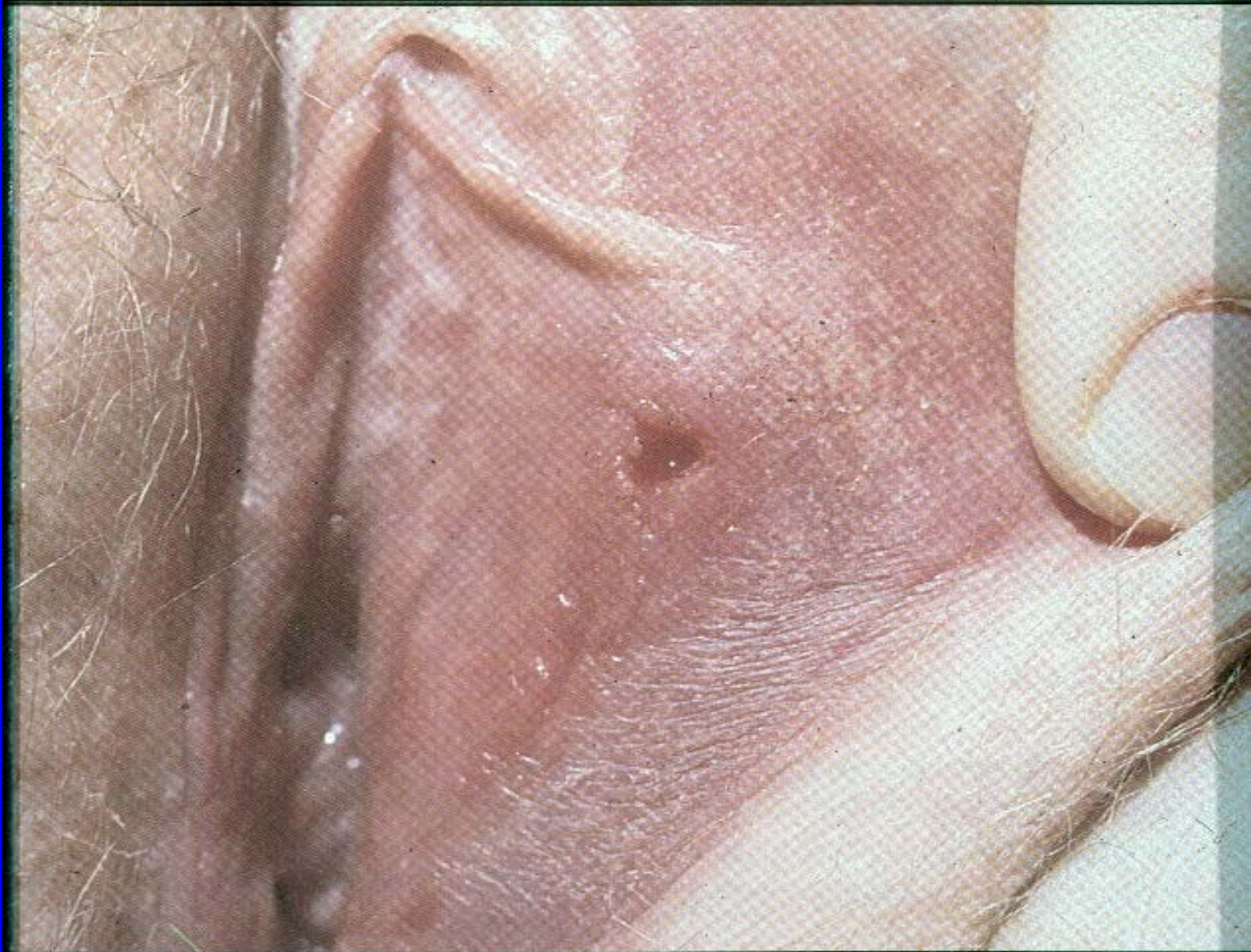
Genital Ulcer Disease: Diagnosis

- **Diagnosis based on medical history and exam alone is often inaccurate**
- **Tests for patients with ulcers:**
 - **Serology and/or darkfield/DIF testing for syphilis**
 - **Culture or antigen test for HSV**
 - **Culture for *Hemophilus ducreyi***
- **HIV testing should be offered**
- **Treatment may need to be empiric, especially for interruption of transmission**
 - **Some experts advocate empiric therapy, if diagnosis unclear, against syphilis**

HSV Infection

- **Clinical diagnosis both insensitive and nonspecific**
- **Evaluation of genital ulcers best done by swab at ulcer base**
 - **Sensitivity of culture declines rapidly as lesions begin to heal**
 - **PCR assays for HSV-DNA are commercially available, in addition to culture: more sensitive than culture**
- **Serologic tests**
 - **Almost all HSV-2 infections are sexually transmitted**
 - **Newer assays are available that can distinguish HSV- 1 from HSV-2---but IgG antibodies ONLY**





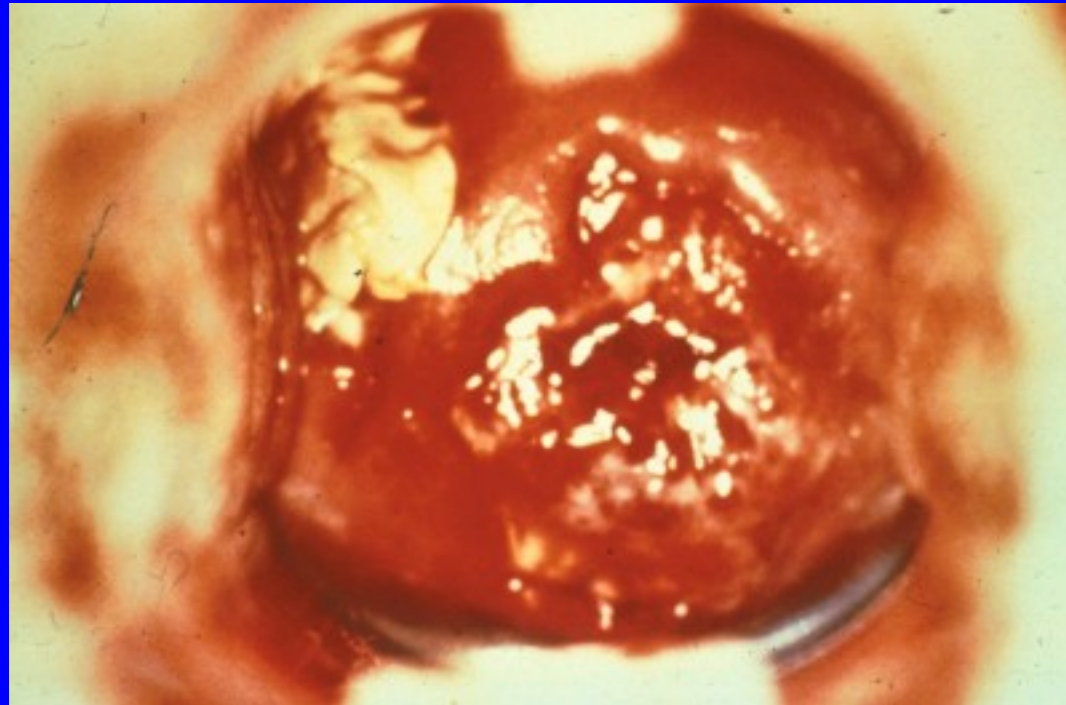
Primary herpes, female



Same patient, four days later



Herpes cervicitis



HSV Assays (1)

- **Both type-specific and nontype-specific antibodies to HSV develop during the first several weeks after infection and persist indefinitely**
- **Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1).**
 - **Such assays first became commercially available in 1999, but older assays that do not accurately distinguish HSV-1 from HSV-2 antibody (despite claims to the contrary) remain on the market.**
 - **Therefore, the serologic type-specific glycoprotein G (gG)-based assays should be specifically requested when serology is performed**

HSV Assays (2)

The FDA-cleared glycoprotein G-based type-specific assays include:

- Laboratory-based assays
 - HerpeSelect™-1 or HerpeSelect™-2 ELISA IgG
 - HerpeSelect™1 and 2 Immunoblot IgG (Focus Technology, Inc., Herndon, VA)
 - HSV-2 ELISA (Trinity Biotech USA, Berkeley Heights, NJ).
- Point-of-care assays (capillary blood or serum at a clinic visit)
 - Biokit HSV-2 (Biokit USA, Lexington, MA)
 - SureVue HSV-2, (Fisher Scientific, Pittsburgh, PA)

The sensitivities of these glycoprotein G type-specific tests for the detection of HSV-2 antibody vary from 80%–98%, and false-negative results might be more frequent at early stages of infection. *MMWR 8/06*

HSV Screening: CDC 8/06

Type-specific HSV serologic assays might be useful in the following scenarios:

- 1) recurrent genital symptoms or atypical symptoms with negative HSV cultures
- 2) a clinical diagnosis of genital herpes without laboratory confirmation
- 3) a partner with genital herpes (esp. in pregnancy?)

Screening for HSV-1 or HSV-2 in the general population is not indicated.

HSV: Treatment

- Treatment can control symptoms when used for first or recurrent clinical episodes or for suppression, but does not eradicate latent virus.
- Randomized trials indicate that three antivirals provide clinical benefit:
 - Acyclovir
 - Valacyclovir
 - Famcyclovir
- Topical therapy for HSV, with antiviral or other drugs, has not been shown to offer any clinical benefit, “and its use is discouraged”

HSV Treatment Regimens

(update CDC, 8/06)

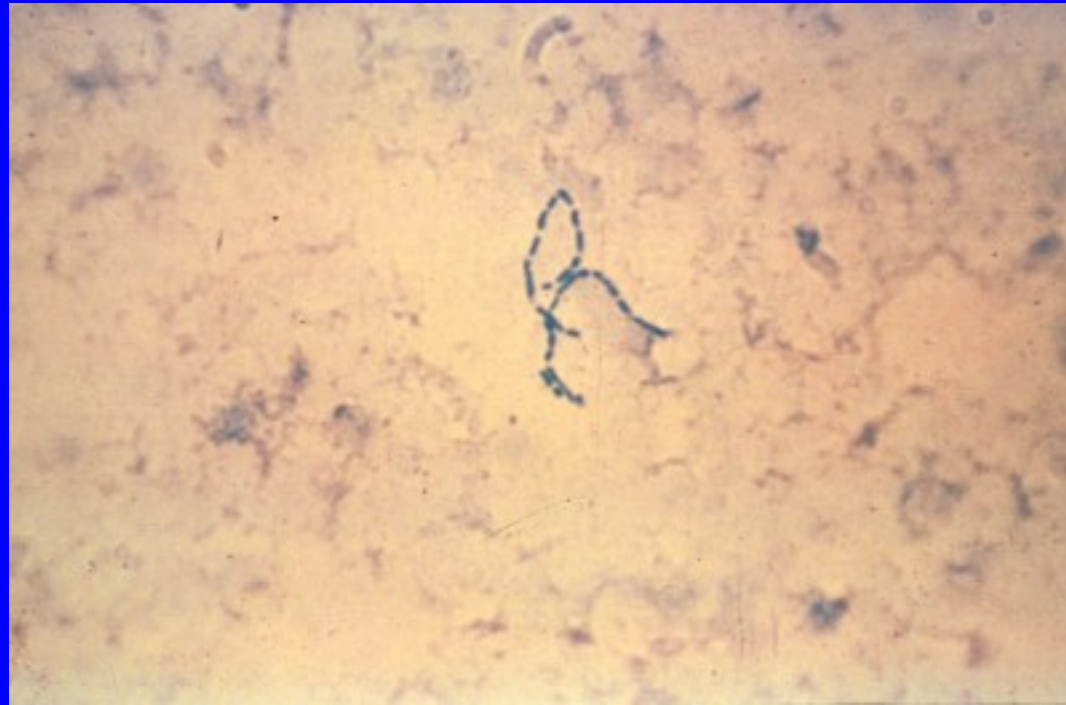
<u>Indication</u>	<u>Acyclovir</u>	<u>Valacyclovir</u>	<u>Famcyclovir</u>
First clinical episode (Rx 7-10d)	400 mg TID or 200 mg 5x/d	1 gm BID	250 mg TID
Recurrent episode (Rx 5 d)	400 mg TID or 800 mg BID or 800 mg TID, 2d	500 mg BID, 3d or 1 gm QD, 5d	125 mg BID or 1 gm BID, 1 d
Suppression (daily)	400 mg BID	500 mg QD* or 1 gm QD	250 mg BID

* Less effective in pts with very frequent recurrences

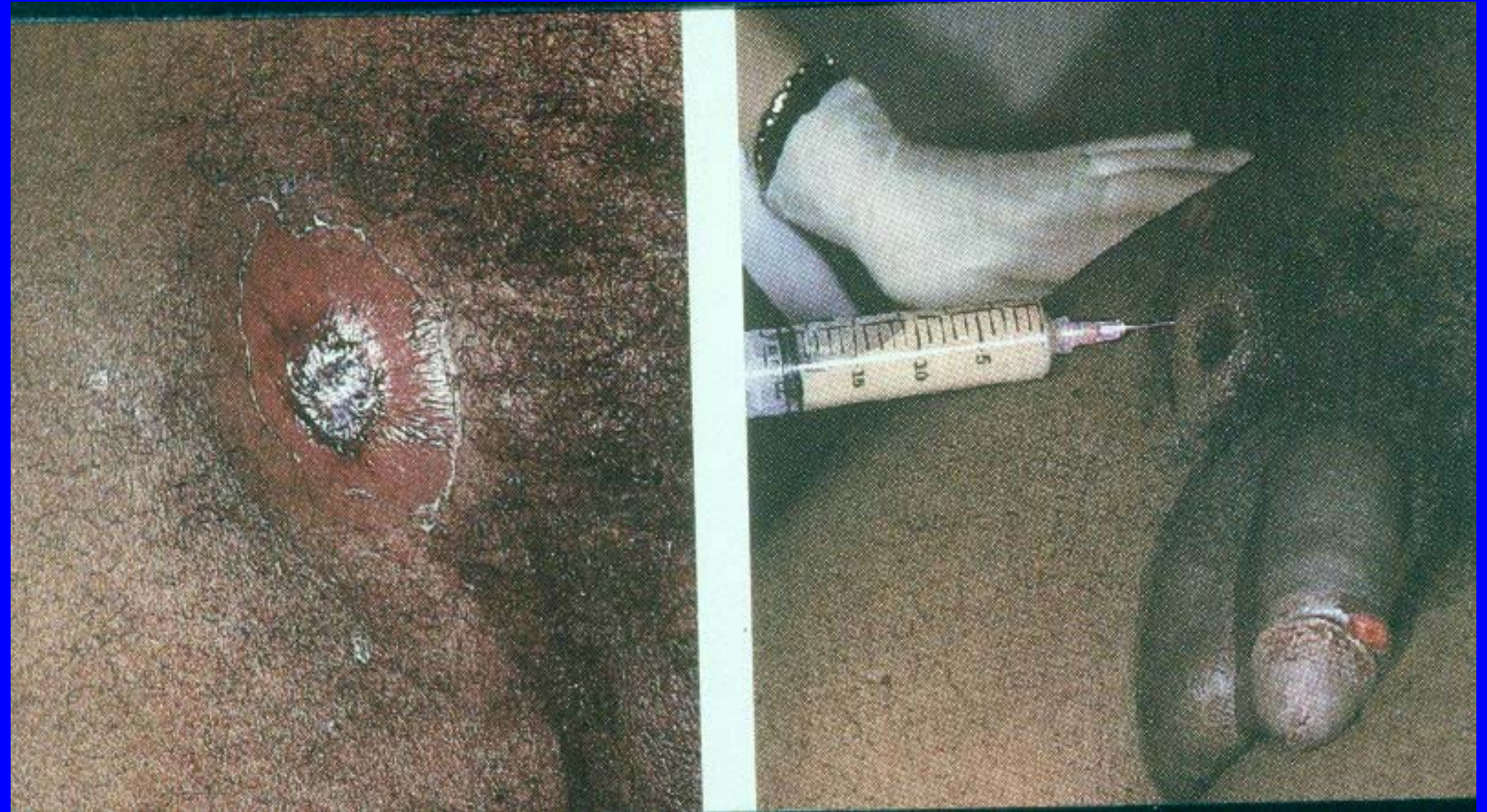
Genital Ulcer Diseases: Chancroid

- **Characterized by**
 - **Painful ulcers (more commonly multifocal in women), almost always genital/perianal**
 - **Tender inguinal lymphadenopathy common (50%)**
 - **Suppurative inguinal lymphadenopathy (bubo) and genital ulcers pathognomonic of chancroid**
 - . **Bubo can rupture and form chronic draining sinuses**
- **Diagnosed by culture of material by swab from ulcer base or by bubo aspiration**
 - **Need to request special culture media**
 - **PCR analyses being evaluated: no FDA-approved PCR test for *H. ducreyi* available in US**

Chancroid - gram stain of *H.*
ducreyi



Chancroid



Chancroid: Treatment

- Azithromycin 1 gm po x 1
- Ceftriaxone 250 mg IM x 1
- Ciprofloxacin 500 mg po BID x 3 d*
- Erythromycin base 500 mg po TID x 7d*

**Worldwide, several isolates with intermediate resistance have been reported*

Ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no improvement, need to consider: (1) diagnosis, (2) coinfection with another STD, (3) noncompliance with rx, (4) resistant strain

Genital Ulcer Disease: Granuloma Inguinale

- Also called Donovanosis - caused by *Calymmatobacterium granulomatis*, which produce typical “Donovan bodies” microscopically (biopsy).
- Rare in the U.S., but endemic in tropical/developing areas: India, Papua New Guinea, central Australia, southern Africa, SE Asia
- Begins as small, painless papule that ulcerates to form a beefy-red, friable, granulomatous ulcer (painless)
 - Multiple lesions may coalesce to form large ulcerated areas
 - Spreads subcutaneously with progressive destruction
- Spontaneous healing with extensive scar formation
 - Can produce extensive deformities, including lymphedema/elephantiasis

Granuloma inguinale, male



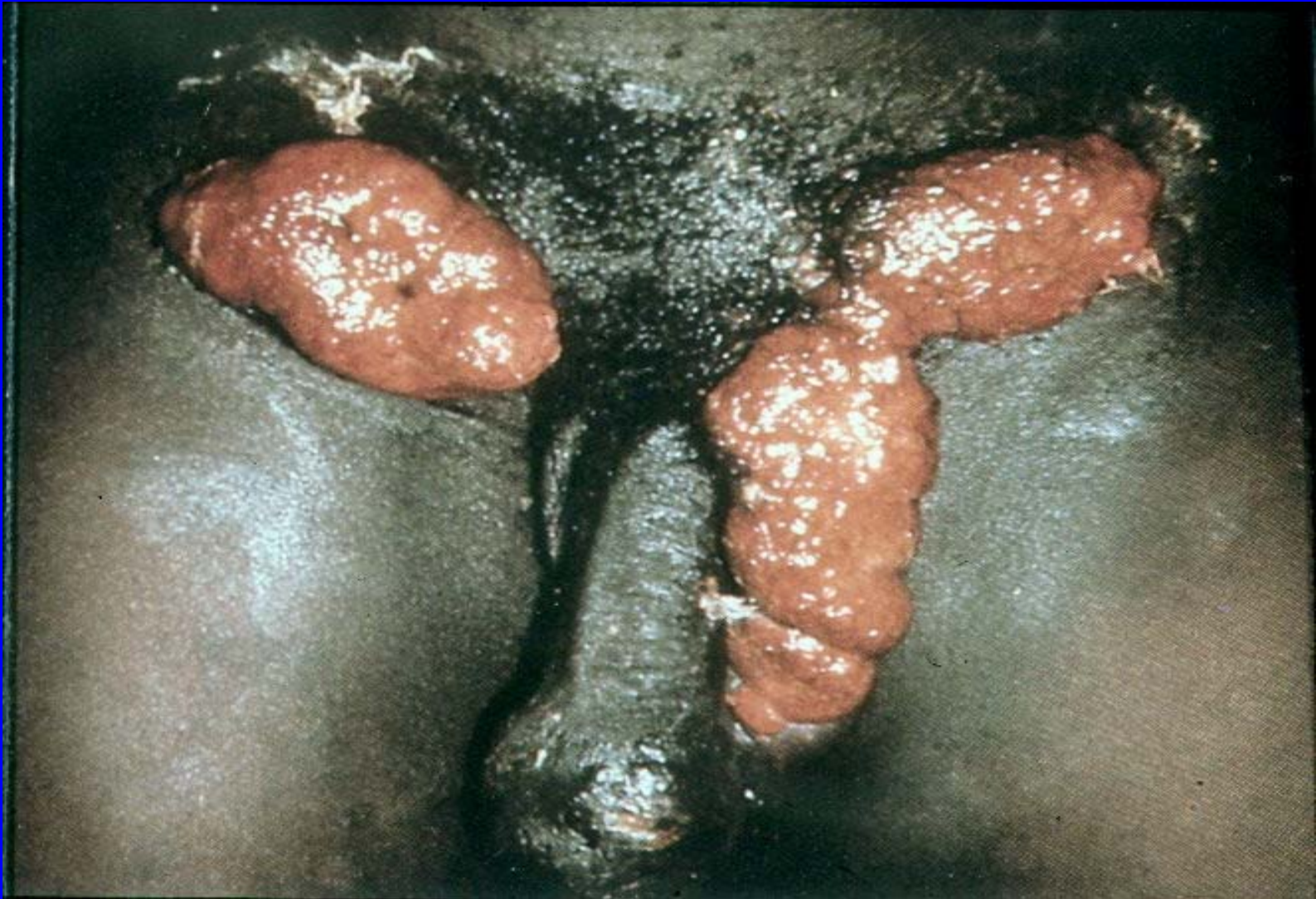
Granuloma inguinale, female



Granuloma inguinale with both active and healed lesions



Granuloma Inguinale



Granuloma Inguinale: Diagnosis/Treatment

- Organism difficult to culture, and diagnosis requires special staining of tissue biopsy
- Treatment appears to halt progress of lesions, but prolonged therapy needed, and relapse can occur 6-18 months after apparently effective therapy
- Recommended (for at least 3 weeks, & until all lesions healed)
 - Doxycycline 100 mg po BID
- Alternatives (for at least 3 weeks)
 - Ciprofloxacin 750 mg po BID
 - Erythromycin base 500 mg po QI
 - Azithromycin 1 gm po Q week
 - TMP-SMX, 1 - DS po BID
- Some experts add aminoglycoside (IV) if not improved after 3-5 days of therapy

STD Evaluation: **Sexual Assault**

- **Cultures for NG and CT collected from any sites of (attempted) penetration**
- **If chlamydial culture not available, FDA-approved nucleic acid tests are acceptable. Positive test should be confirmed with a 2nd FDA-licensed nucleic acid test that targets a different sequence**
- **EIA, non-amplified probes, and DFA not acceptable alternatives: false (-) rates much higher**
- **Wet mount/culture for trichomonas (and BV/candida if discharge/symptoms)**
- **Serum testing for HIV, HBV, syphilis**

Sexual Assaults: **STD Prophylaxis**

- **Post-exposure HBV vaccination, generally without HBIG**
 - **Empiric treatment for CT, GC, trichomonas, BV may be administered:**
 - **Ceftriaxone 125 mg IM x 1**
 - **Metronidazole 2 gm po x 1**
 - **Azithromycin 1 gm po x 1**
- OR**
- **Doxycycline 100 mg po BID x 7d**