STDS AND HIV

Chlamydia, Gonorrhea, Genital Human Papilomavirus, Herpes Simples and Syphillis

Presented on October 7, 2010 at
MCRH's Parallel Paths Lunch and Learn for HIV/AIDS Providers
Supported through a generous grant from the MAC AIDS Fund

Parallel Paths Project

- A series of training sessions on topics of reproductive health for HIV/AIDS social and medical service providers
- Find more and updated information at: http://mcrh-tn.org/outreach_parallel_paths.asp
- Funding for this project provided by the MAC AIDS Fund.

Chlamydia

Chlamydia trachomatis

Incidence and Cost

- Estimated 3 million new cases in U.S. annually
- Most frequently reported disease in U.S.
- Estimated annual incidence of selected STDs:
  - Trichomoniasis — 7.4 million
  - Human Papillomavirus (HPV) — 6.2 million
  - Herpes Simplex Virus (HSV) — 1.6 million
  - Gonorrhea — 718,000
  - Syphilis — 37,000
- Direct and indirect annual costs total approximately $2.4 billion

Risk Factors

- Adolescence
- New or multiple sex partners
- History of STD infection
- Presence of another STD
- Oral contraceptive user
- Lack of barrier contraception

Transmission

- Transmission is **sexual** or **vertical**
- Highly transmissible
- Incubation period 7-21 days
- Significant asymptomatic reservoir
- Re-infection is common
- Perinatal transmission results in neonatal conjunctivitis in 30%-50% of exposed babies

Clinical Syndromes Caused by *C. trachomatis*

	Local Infection	Complication	Sequelae
Men	Conjunctivitis Urethritis Proctitis	Epididymitis Reiter's syndrome (rare)	Infertility (rare) Chronic arthritis (rare)
Women	Conjunctivitis Urethritis Cervicitis Proctitis	Endometritis Salpingitis Perihepatitis Reiter's syndrome (rare)	Infertility Ectopic pregnancy Chronic pelvic pain Chronic arthritis (rare)
Infants	Conjunctivitis Pneumonitis Pharyngitis Rhinitis	Chronic lung disease?	Rare, if any

C. trachomatis Infection in Men

- Urethritis–One cause of non-gonococcal urethritis (NGU)
  - Majority (>50%) asymptomatic
  - Symptoms/signs if present: mucopurulent, mucoid or clear urethral discharge, dysuria
  - Incubation period unknown (probably 5-10 days in symptomatic infection)

Non-Gonococcal Urethritis: Mucoid Discharge

Source: Seattle STD/HIV Prevention Training Center at the University of Washington/UW HSCER Slide Bank

C. trachomatis Complications in Men

- Epididymitis
- Reiter's Syndrome

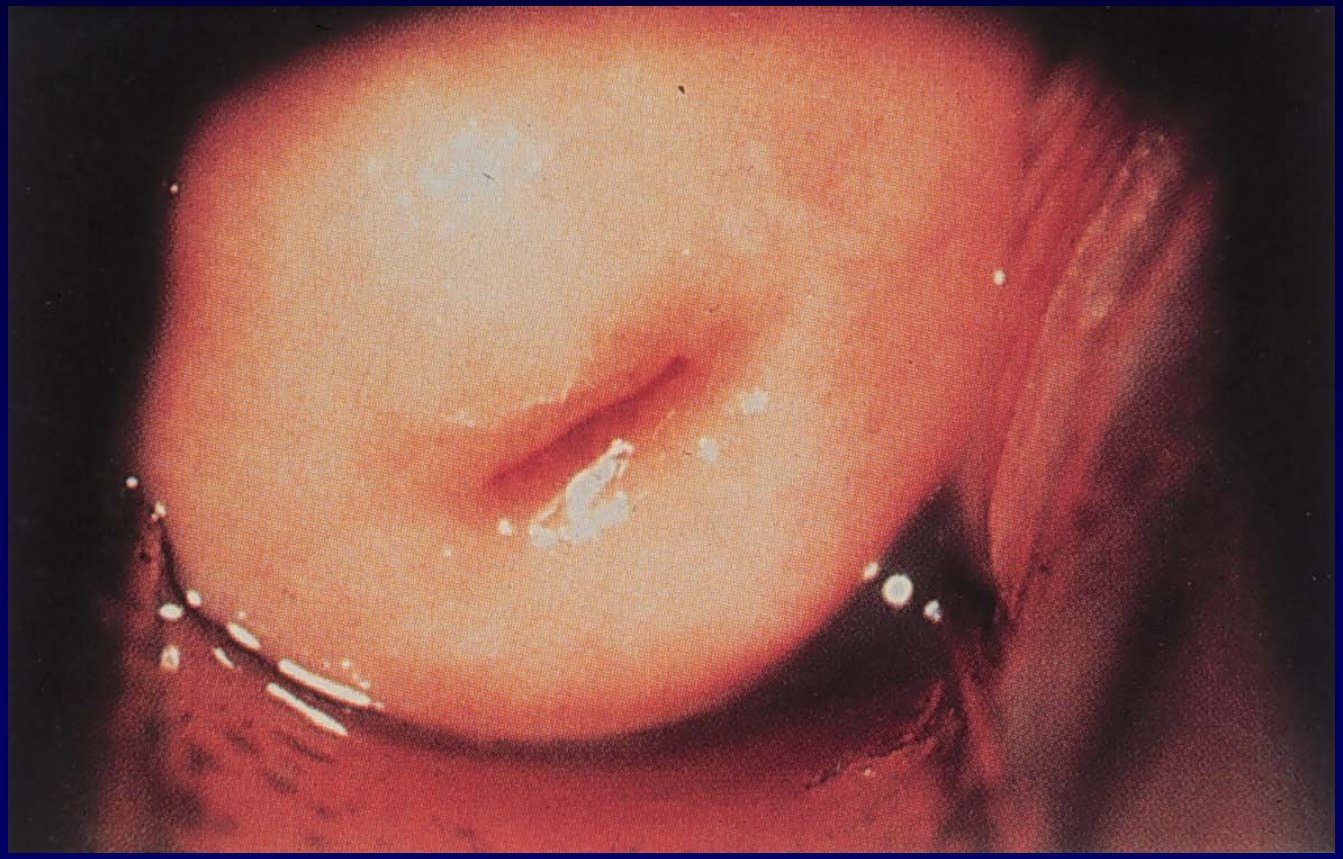
Swollen or tender testicles (epididymitis)

Source: Seattle STD/HIV Prevention Training Center at the University of Washington

C. trachomatis Infections in Women

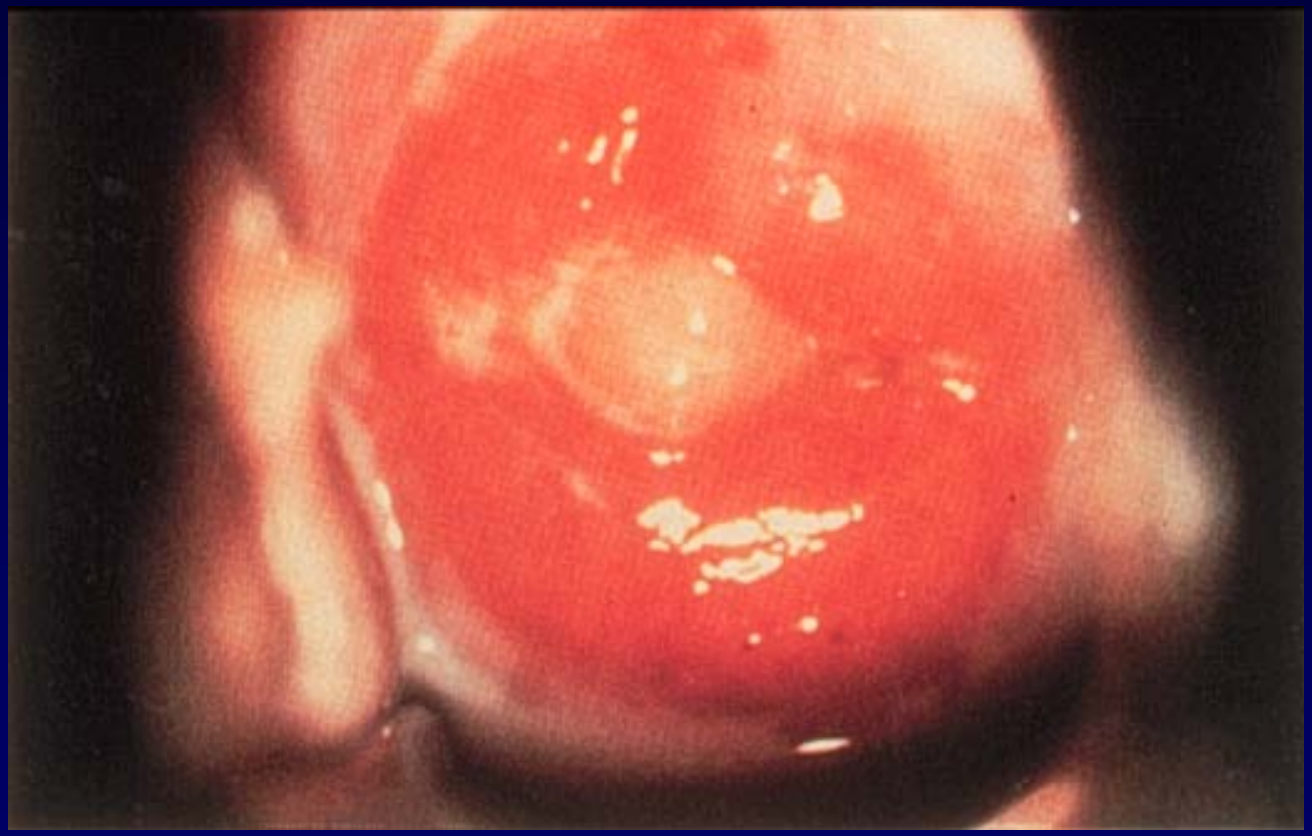
- Cervicitis
  - Majority are asymptomatic
  - Local signs of infection, when present, include:
    - Mucopurulent endocervical discharge
    - Edematous cervical ectopy with erythema and friability
- Urethritis
  - Usually asymptomatic
  - Signs/symptoms, when present, include dysuria, frequency, pyuria

Normal Cervix



Source: STD/HIV Prevention Training Center at the University of Washington/Claire E. Stevens

Chlamydial Cervicitis



Source: STD/HIV Prevention Training Center at the University of Washington/Connie Celum and Walter Stamm

C. trachomatis Complications in Women

- Pelvic Inflammatory Disease (PID)
  - Salpingitis
  - Endometritis
- Perihepatitis (Fitz-Hugh-Curtis Syndrome)
- Reiter's Syndrome

Treatment of Uncomplicated Genital Chlamydial Infections

CDC-recommended regimens

- Azithromycin 1 g orally in a single dose, OR
- Doxycycline 100 mg orally twice daily for 7 days

Alternative regimens

- Erythromycin base 500 mg orally 4 times a day for 7 days, OR
- Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, OR
- Ofloxacin 300 mg orally twice a day for 7 days
- Levofloxacin 500 mg orally once a day for 7 days

Treatment of Chlamydial Infection in Pregnant Women

CDC-recommended regimens

- Azithromycin 1 g orally in a single dose, OR
- Amoxicillin 500 mg orally 3 times a day for 7 days

Alternative regimens

- Erythromycin base 500 mg orally 4 times a day for 7 days, OR
- Erythromycin base 250 mg orally 4 times a day for 14 days, OR
- Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, OR
- Erythromycin ethylsuccinate 400 mg orally 4 times a day for 14 days, OR

Treatment of Lymphogranuloma Venereum (LGV)

CDC-recommended regimen

- Doxycycline 100 mg orally twice a day for 21 days

Alternative regimen

- Erythromycin base 500 mg orally 4 times a day for 21 days

Gonorrhea

Neisseria gonorrhoeae

Genital Infection in Men

- Urethritis – Inflammation of urethra
- Epididymitis – Inflammation of the epididymis

Male Urethritis

- Symptoms
  - Typically purulent or mucopurulent urethral discharge
  - Often accompanied by dysuria
  - Discharge may be clear or cloudy
- Asymptomatic in 10% of cases
- Incubation period: usually 1-14 days for symptomatic disease, but may be longer

Gonococcal Urethritis: Purulent Discharge

Source: Seattle STD/HIV Prevention Training Center at the University of Washington: Connie Celum and Walter Stamm

Epididymitis

- Symptoms: unilateral testicular pain and swelling
- Infrequent, but most common local complication in males
- Usually associated with overt or subclinical urethritis

Genital Infection in Women

- Most infections are asymptomatic
- Cervicitis – inflammation of the cervix
- Urethritis – inflammation of the urethra

Cervicitis

- Non-specific symptoms: abnormal vaginal discharge, intermenstrual bleeding, dysuria, lower abdominal pain, or dyspareunia
- Clinical findings: mucopurulent or purulent cervical discharge, easily induced cervical bleeding
- 50% of women with clinical cervicitis have no symptoms
- Incubation period unclear, but symptoms may occur within 10 days of infection

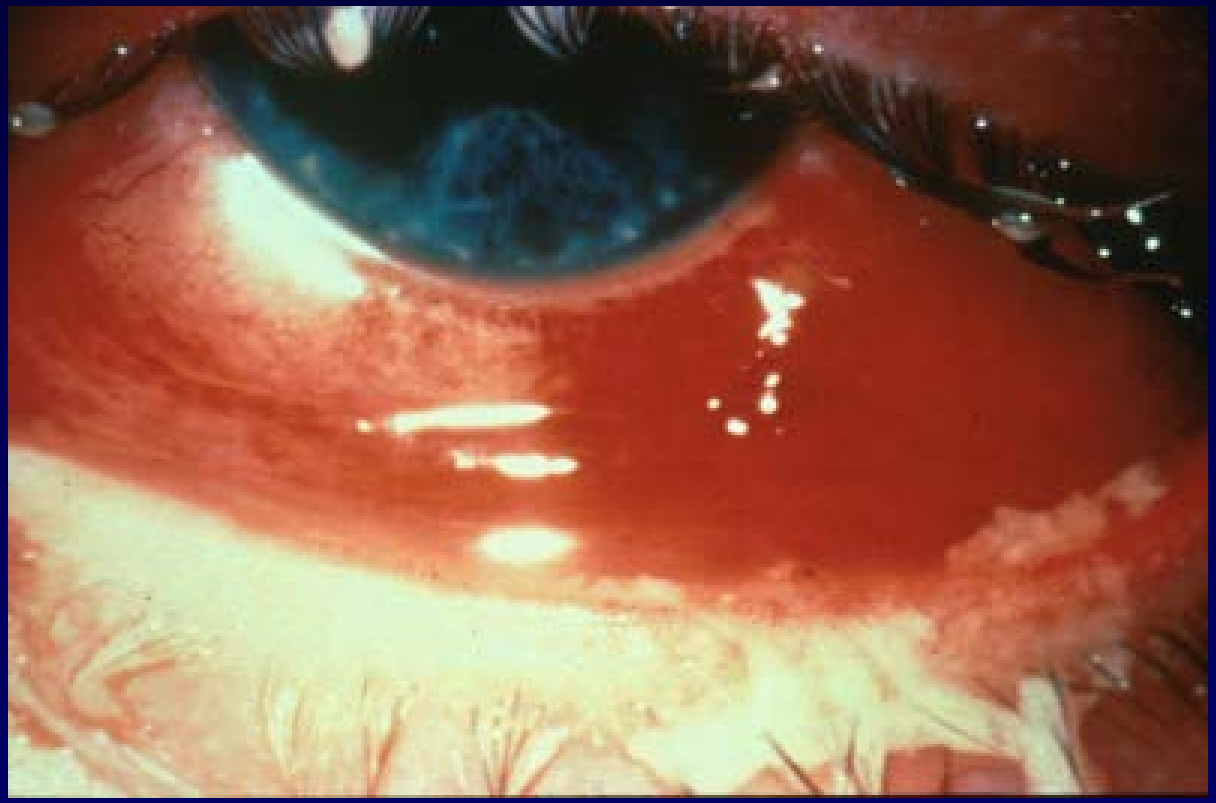
Urethritis

- Symptoms: dysuria, however, most women are asymptomatic
- 40%-60% of women with cervical gonococcal infection may have urethral infection

Complications in Women

- Accessory gland infection
  - Bartholin's glands
  - Skene's glands
- Pelvic Inflammatory Disease (PID)
  - May be asymptomatic
  - May present with lower abdominal pain, discharge, dyspareunia, irregular menstrual bleeding and fever
- Fitz-Hugh-Curtis Syndrome
  - Perihepatitis

Gonococcal Ophthalmia



Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Disseminated Gonorrhea—Skin Lesion

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Treatment for Uncomplicated Infections of the Cervix, Urethra, and Rectum

Ceftriaxone	125mg	IM	Once or
Cefixime	400mg	Orally	Once or

[1] Contraindicated in pregnancy and children. Not recommended for infections acquired in California, Asia, or the Pacific, including Hawaii.

Co-treatment for *Chlamydia trachomatis*

If chlamydial infection is not ruled out:

Azithromycin	1 g	Orally	Once or
Doxycycline	100 mg	Orally	Twice a day for 7 days

Syphilis

Treponema pallidum

Transmission

- Sexual and vertical
- Most contagious to sex partners during the primary and secondary stages

Treponema pallidum

Electron photomicrograph, 36,000 x.

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Treponema pallidum on darkfield microscopy

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Pathology

- Penetration:
  - *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
  - Transmitted transplacentally from mother to fetus during pregnancy
- Dissemination:
  - Travels via the lymphatic system to regional lymph nodes and then throughout the body via the blood stream
  - Invasion of the CNS can occur during any stage of syphilis

Primary Syphilis

- Primary lesion or "chancre" develops at the site of inoculation
- Chancre:
  - Progresses from macule to papule to ulcer
  - Typically painless, indurated, and has a clean base
  - Highly infectious
  - Heals spontaneously within 1 to 6 weeks
  - 25% present with multiple lesions
- Regional lymphadenopathy: classically rubbery, painless, bilateral
- Serologic tests for syphilis may not be positive during early primary syphilis

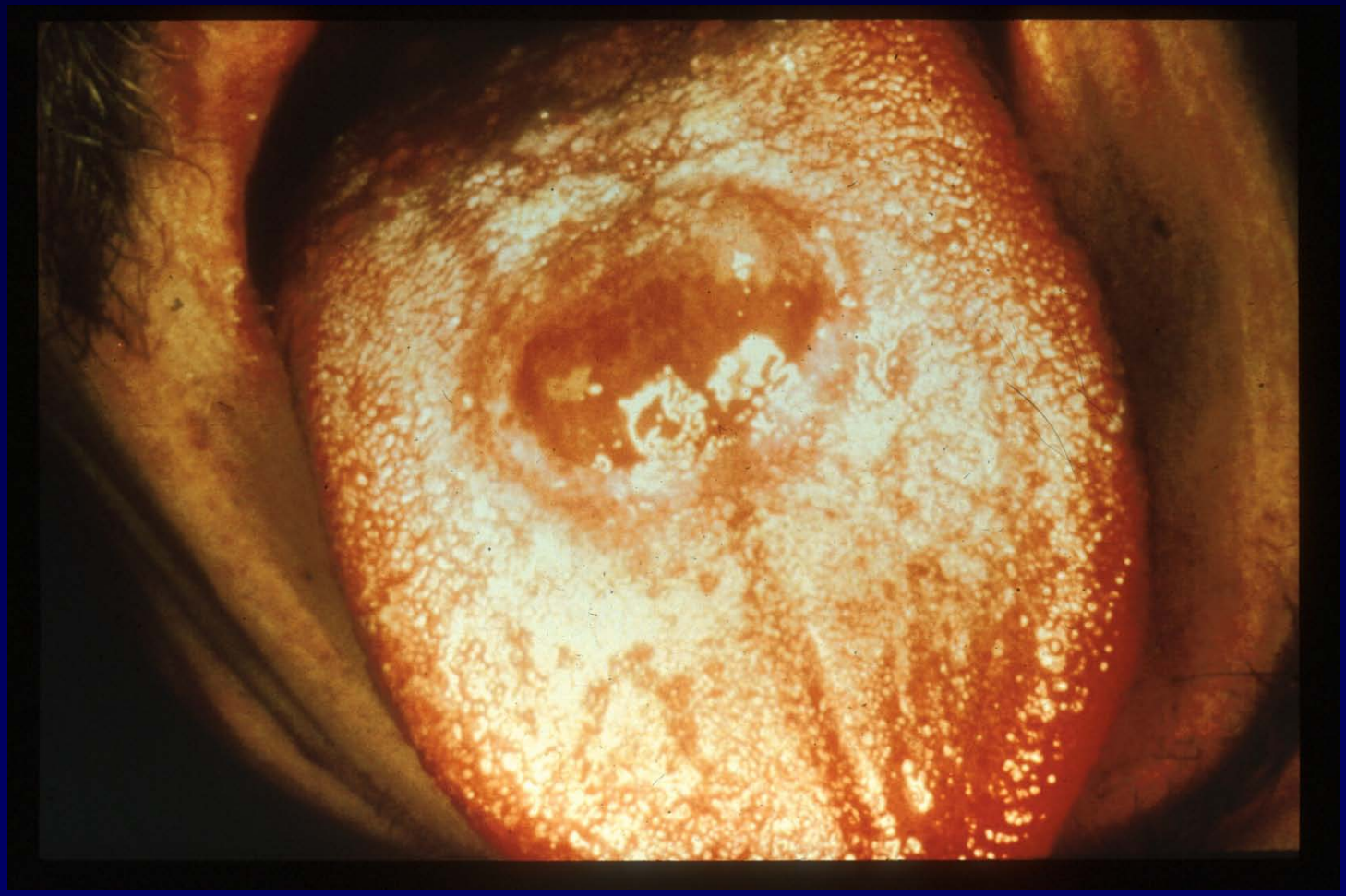
Primary Syphilis- Penile Chancre

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Primary Syphilis – Labial Chancre

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Syphilis Lesion - Tongue



Source: CDC/ NCHSTP/ Division of STD Prevention /STD Clinical Slides

Secondary Syphilis

- Secondary lesions occur 3 to 6 weeks after the primary chancre appears; may persist for weeks to months
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Manifestations:
  - Rash (75%-100%)
  - Lymphadenopathy (50%-86%)
  - Malaise
  - Mucous patches (6%-30%)
  - Condylomata lata (10%-20%)
  - Alopecia (5%)
- Serologic tests are usually highest in titer during this stage

Secondary Syphilis - Papulosquamous Rash

Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

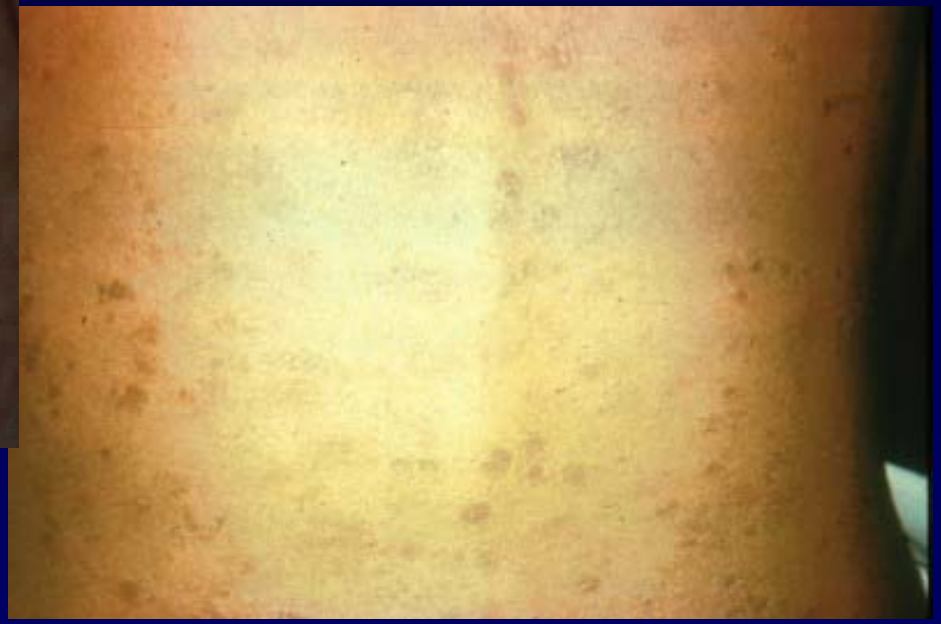
Secondary Syphilis: Palmar/Plantar Rash

Source: Seattle STD/HIV Prevention Training Center at the University of Washington, UW HSCER Slide Bank

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis: Generalized Body Rash

Source: Cincinnati STD/HIV Prevention Training Center



Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Latent Syphilis

- Host suppresses infection-no lesions are clinically apparent
- Only evidence is positive serologic test
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
  - Early latent: <1 year duration
  - Late latent: ≥1 year duration

Neurosyphilis

- Occurs when *T. pallidum* invades the CNS
- May occur at any stage of syphilis
- Can be asymptomatic
- Early neurosyphilis occurs a few months to a few years after infection
  - Clinical manifestations include acute syphilitic meningitis, meningovascular syphilis, ocular involvement
- Late neurosyphilis occurs decades after infection and is rarely seen
  - Clinical manifestations include general paresis, tabes dorsalis, ocular involvement

Diagnosis of Latent Syphilis

- Criteria for early latent syphilis:
  - Documented seroconversion or 4-fold increase in comparison with a serologic titer obtained within the year preceding the evaluation
  - Unequivocal symptoms of primary or secondary syphilis reported by patient in past 12 months
  - Contact to an infectious case of syphilis
  - Only possible exposure occurred within past 12 months
- Patients with latent syphilis of unknown duration should be managed clinically as if they have late latent syphilis.

CNS Disease Diagnostic Issues

- CNS disease can occur during any stage of syphilis.
- Conventional therapy is effective for the vast majority of immuno-competent patients with asymptomatic CNS involvement in primary and secondary syphilis.

Indications for CSF Examination

- Patients with syphilis who demonstrate any of the following criteria should have a prompt CSF evaluation:
  - Neurologic or ophthalmic signs or symptoms,
  - Evidence of active tertiary syphilis (e.g., aortitis, gumma, and iritis),
  - Treatment failure, or
  - HIV infection with late latent syphilis or syphilis of unknown duration.

Diagnosis of CNS Disease

No test can be used alone to diagnose neurosyphilis.

- VDRL-CSF: highly specific but insensitive
- Diagnosis usually depends on the following factors:
  - Reactive serologic test results,
  - Abnormalities of CSF cell count or protein, or
  - A reactive VDRL-CSF with or without clinical manifestations.
- CSF leukocyte count usually is elevated (>5 WBCs/mm^3) in patients with neurosyphilis.
- The VDRL-CSF is the standard serologic test for CSF, and when reactive in the absence of contamination of the CSF with blood, it is considered diagnostic of neurosyphilis.

Effect of HIV Infection on Syphilis

- Syphilis and HIV infections commonly coexist.
- Clinical course is similar to non-HIV-infected patients.
- Serological tests are usually equivalent in sensitivity in HIV-infected and non-infected persons.
- Conventional therapy is usually effective.
- HIV-infected patients may be more likely to present with symptomatic neurosyphilis.

Therapy for Primary, Secondary, and Early Latent Syphilis

- Benzathine penicillin G 2.4 million units IM in a single dose (Bicillin L-A®)
- If penicillin allergic:
  - Doxycycline 100 mg orally twice daily for 14 days, or
  - Tetracycline 500 mg orally 4 times daily for 14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55 (No. RR-11).

Therapy for Late Latent Syphilis or Latent Syphilis of Unknown Duration

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
- If penicillin allergic:
  - Doxycycline 100 mg orally twice daily for 28 days OR
  - Tetracycline 500 mg orally 4 times daily for 28 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55 (No. RR-11).

Therapy for Tertiary Syphilis without Neurologic Involvement

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
- Penicillin allergic:
  - Doxycycline 100 mg orally twice daily for 28 days OR
  - Tetracycline 500 mg orally 4 times daily for 28 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR 2006;55 (No. RR-11).

Therapy for Neurosyphilis

- Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion for 10-14 days IV
- Alternative regimen (if compliance can be ensured):
  - Procaine penicillin 2.4 million units IM once daily PLUS Probenecid 500 mg orally 4 times a day, both for 10-14 days

Source: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. MMWR 2006;55 (No. RR-11).

Syphilis and HIV/Other STDs

- Penicillin-allergic patients with syphilis and HIV whose compliance cannot be ensured should be desensitized and treated with penicillin.
- All patients who have syphilis should be tested for HIV infection.
- Consider screening persons with syphilis for other STDs based on risk.

Genital and Perirectal Herpes Simplex Virus Infection

Herpes Simplex Virus (HSV) Type 2

Background and Burden of Disease

- Genital herpes is a chronic, lifelong viral infection
- Two HSV serotypes – HSV-1 & HSV-2
- HSV-2 causes the majority of cases of recurrent genital herpes in the U.S.
- Approximately 1 million new cases occur each year

Background and Burden of Disease (continued)

- In the U.S., 17% of adults aged 14-49 years have HSV-2 antibodies
- HSV-2 antibodies are not routinely detected until puberty
- HSV-2 seroprevalence is higher in women than men in all age groups and varies by race/ethnicity

Transmission

- HSV-2 is transmitted sexually and perinatally
- Majority of genital herpes infections are transmitted by persons who are
  - unaware they are infected with HSV-2 or
  - asymptomatic when transmission occurs
- Efficiency of sexual transmission is greater from men to women than from women to men

Transmission (continued)

- Likelihood of transmission declines with increased duration of infection
- Incubation period after acquisition is 2-12 days (average is 4 days)
- Drying and soap and water readily inactivate HSV; fomite transmission unlikely

HSV-2 and HIV Infection

- HSV-2 infection increases the risk of acquiring HIV infection at least 2 fold
- HSV-2 infection is also likely to facilitate transmission of HIV infection from persons co-infected with both viruses

Definitions of Infection Types

First Clinical Episode

- Primary infection
  - First infection **ever** with either HSV-1 or HSV-2
  - No antibody present when symptoms appear
  - Disease is more severe than recurrent disease

- Non-primary infection
  - Newly acquired HSV-1 or HSV-2 infection in an individual previously seropositive to the other virus
  - Symptoms usually milder than primary infection
  - Antibody to new infection may take several weeks to a few months to appear

Definitions of Infection Types

Recurrent symptomatic infection

- Antibody present when symptoms appear
- Disease usually mild and short in duration

Asymptomatic infection

- Serum antibody is present
- No known history of clinical outbreaks

Genital Herpes: Primary Lesions

Source: Cincinnati STD/HIV Prevention Training Center

Genital Herpes: Recurrent Ulcer

Source: Cincinnati STD/HIV Prevention Training Center

Genital Herpes: Periurethal Lesions

Source: Cincinnati STD/HIV Prevention Training Center

Herpes on the Buttock

Source: Cincinnati STD/HIV Prevention Training Center

Asymptomatic Viral Shedding

- Most HSV-2 is transmitted during asymptomatic shedding
- Rates of asymptomatic shedding greater in HSV-2 than HSV-1
- Rates of asymptomatic shedding are highest in new infections (<2 years) and gradually decrease over time
- Asymptomatic shedding episodes are of shorter duration than shedding during clinical recurrences

Asymptomatic Viral Shedding
(continued)

- Most common sites of asymptomatic shedding are vulva and perianal areas in women and penile skin and perianal area in men
- Antiviral suppressive therapy dramatically reduces, but does not eradicate shedding

Severe Disease

- IV acyclovir should be provided for patients with severe disease or complications requiring hospitalization

- CDC-Recommended Regimen:
  - Acyclovir 5-10 mg/kg IV every 8 hours for 2-7 days or until clinical improvement
  - Follow with oral antiviral therapy to complete at least 10 days total therapy

Herpes in HIV-Infected Persons

- HIV-infected persons may have prolonged, severe, or atypical episodes of genital, perianal, or oral herpes
- HSV shedding is increased in HIV-infected persons

CDC-Recommended Regimens for Daily Suppressive Therapy in HIV-Infected Persons

- Acyclovir 400-800 mg orally twice a day or three times a day, or
- Famciclovir 500 mg orally twice a day, or
- Valacyclovir 500 mg orally twice a day

CDC-Recommended Regimens for Episodic Infection in HIV-Infected Persons

- Acyclovir 400 mg orally 3 times a day for 5-10 days, or
- Famciclovir 500 mg orally twice a day for 5-10 days, or
- Valacyclovir 1 g orally twice a day for 5-10 days

Genital Human Papillomavirus (HPV)

Introduction

- Genital HPV is one of the most common STDs.
- More than 30 HPV types can infect the genital tract.

Introduction

- HPV types are divided into 2 groups based on their association with cervical cancer:
  - Low-risk types associated with genital warts and mild Pap test abnormalities
  - High-risk types associated with mild to severe Pap test abnormalities and cervical cancer
- Most genital HPV infections are transient, asymptomatic, and have no clinical consequences.

Incidence in the U.S.

- Estimated annual incidence of sexually transmitted HPV infection is 6.2 million
- Estimated $1.6 billion spent annually in direct medical costs to treat symptoms of genital HPV infection
- Estimated 20 million people currently have a detectable genital HPV infection

HPV Genotyping System

- Low-risk types
  - Most visible warts caused by HPV types 6 and 11
  - Recurrent respiratory papillomatosis associated with HPV types 6 and 11
- High-risk types
  - HPV types 16 and 18 found in more than half of anogenital cancers
  - Most women with high-risk HPV infection have normal Pap test results and never develop precancerous cell changes or cervical cancer

Natural History of HPV

- Most genital HPV infections are transient, asymptomatic, or subclinical, and have no clinical consequences in immunocompetent individuals.
- The incubation period is unclear.
- The median duration of new cervical infections is 8 months but varies by type.
- Gradual development of an effective immune response is the likely mechanism for HPV DNA clearance.

Natural History of HPV (continued)

- **Persistent infection** is infection that is not cleared by the immune system and is characterized by persistently detectable HPV DNA.
  - HPV infection that persists is the most important factor for precancerous cervical cell changes and cervical cancer.
  - Most women with persistent HPV infection do not develop cervical cancer precursors or cervical cancer.

Clinical Manifestations and Sequelae

- In most cases, genital HPV infection is transient and has no clinical manifestations or sequelae.
- Clinical manifestations of genital HPV infection include:
  - Genital warts
  - Cervical cell abnormalities
  - Anogenital squamous cell cancers
  - Recurrent respiratory papillomatosis
- Most common clinically significant HPV infection manifestations:
  - Genital warts
  - Cervical cell abnormalities

Genital Warts: Appearance

- Condylomata acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally non-keratinized on mucosal surfaces
- Smooth papules
  - Usually dome-shaped and skin-colored
- Flat papules
  - Macular to slightly raised
  - Flesh-colored, with smooth surface
  - More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
- Keratotic warts
  - Thick horny layer that can resemble common warts or seborrheic keratosis

Genital Warts: Location

- Warts commonly occur in areas of coital friction.
- Perianal warts do not necessarily imply anal intercourse.
  - May be secondary to autoinoculation, sexual activity other than intercourse, or spread from nearby genital wart site.
- Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
- Patients with visible warts can be simultaneously infected with multiple HPV types.

Genital Warts: Symptoms

- Genital warts usually cause no symptoms other than the warts themselves.
- Vulvar warts--dyspareunia, pruritis, burning discomfort
- Penile warts--occasional itching
- Urethral meatal warts--occasional hematuria or impairment of urinary stream
- Vaginal warts--usually asymptomatic; occasional discharge/bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy)
- Perianal warts--usually asymptomatic; pain, bleeding on defecation, itching
- Most patients have fewer than 10 genital warts, with total wart area of 0.5-1.0 $cm^{2.}$

Genital Warts: Duration

- May regress spontaneously or persist with or without proliferation.
  - Frequency of spontaneous regression is unclear.
  - Persistence of infection occurs, but frequency and duration are unknown.
  - Recurrences after treatment are common.

Perianal Warts

Source: Seattle STD/HIV Prevention Training Center at the University of Washington/ UW HSCER Slide Bank

Vulvar Warts

Source: Reprinted with permission of Gordon D. Davis, MD.

Penile Warts

Source: Cincinnati STD/HIV Prevention Training Center

General Treatment of Genital Warts

- Primary goal is removal of symptomatic warts.
- If left untreated, genital warts may regress spontaneously or persist with or without proliferation.
- In most patients, treatment can induce wart-free periods.
- Currently available therapies may reduce, but probably do not eradicate infectivity.
- Effect of current treatment on future transmission is unclear.

Pap Test Screening in Immunodeficient Patients

- Immunodeficiency appears to accelerate intraepithelial neoplasia and invasive cancer.
  - Provide cervical Pap test screening every 6 months for 1 year, then annually for all HIV-infected women with or without genital warts.
  - Anal pap tests and anoscopy: value in absence of symptoms not established, but is under investigation

General Treatment of Genital Warts (continued)

- No evidence that presence of genital warts or their treatment is associated with development of cervical cancer.
- Some patients may choose to forgo treatment and await spontaneous resolution.
- Consider screening persons with newly diagnosed genital warts for other STD (e.g., chlamydia, gonorrhea, HIV, syphilis).

Genital Wart Follow-Up

- Counsel patients to:
  - Watch for recurrences
  - Get regular Pap screening at intervals as recommended for women WITHOUT genital warts
- After visible warts have cleared, follow-up evaluation not mandatory, but provides opportunity to:
  - Monitor or treat complications of therapy
  - Document the absence of warts
  - Reinforce patient education and counseling messages
- Offer patients concerned about recurrences a follow-up evaluation 3 months after treatment.

The Nature of HPV Infection

- Genital HPV infection is common in sexually active adults.
- Incubation period is variable, and it is often difficult to determine the source of infection.
- Natural history of HPV infection is usually benign:
  - Low-risk genital HPV types are associated with mild Pap test abnormalities and genital warts.
  - High-risk types are associated with mild to severe Pap test abnormalities and, rarely, cancers of the cervix, vulva, anus, and penis.
  - Most women infected with high-risk HPV types have no Pap test abnormalities and do not develop cervical cancer.
- Genital warts have a high recurrence rate after treatment.

HPV Vaccines

- Several potential approaches are under investigation.
- The most promising is the use of virus-like particles (VLPs), which preserve native conformations of viral proteins without presence of viral DNA.