Major Causative Agents in STDs

- **Viruses:** HSV (I & II), HPV, Molluscum contagiosum, Hepatitis (A, B, C), CMV, HIV, HTLV
- **Bacteria:** N. gonorrhoea, H. ducreyi (Chancre), Calymmatobacterium granulomatis (Granuloma inguinale), G. vaginalis & other mixed flora (BV, PID), Spirochetes (T. pallidum/syphilis), Chlamydia trachomatis (and LGV), Mycoplasma hominis, Mycoplasma genitalium & Ureaplasma urealyticum (NGU, PID)
- **Protozoa:** Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia
- **Ectoparasites:** Phthirius pubis (crab louse), Sacoptes scabei (Scabies)

Racial and Age Disparities Across Reportable STDs

- African Americans bear a particularly heavy burden
- Blacks represent 14% percent of U.S. but make up:
  - 71% percent of gonorrhea cases (x20, compared to whites)
  - 48% of Chlamydia cases (x8, compared to whites)
  - 52% of syphilis cases (x9, compared to whites)
- Regardless of race or gender, sexually active adolescents and young adults, especially young women, are at increased risk for STDs
- Bias? Minorities are more likely to seek care in public health clinics that report STDs more completely
- Socioeconomic barriers to healthcare and STD prevention likely contribute - access to prevention, screening, treatment, and partner services

STD Treatment Guidelines, 2010

- LGV (C. trachomatis L1-L3)
- Herpes Simplex Viruses
- Syphilis (T. pallidum)
- Chancroid (H. ducreyi)
- Granuloma inguinale (Klebsiella granulomatis)
- Primary HIV Infection
- DDX: Noninfectious causes: trauma, fixed drug eruptions, Behcet's
Characteristics of common ulcerative diseases

<table>
<thead>
<tr>
<th>HSV</th>
<th>Syphilis</th>
<th>Chancroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer</td>
<td>Painful, often</td>
<td>Painful, purulent,</td>
</tr>
<tr>
<td></td>
<td>many, papules</td>
<td>irregular, deep</td>
</tr>
<tr>
<td>LN</td>
<td>Rare except</td>
<td></td>
</tr>
<tr>
<td></td>
<td>primary infxn</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>COMMON</td>
<td></td>
</tr>
<tr>
<td></td>
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</table>

Characteristics of less common ulcerative diseases

<table>
<thead>
<tr>
<th>LGV</th>
<th>Donovanosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer</td>
<td>Small, painless, heal before LAD</td>
</tr>
<tr>
<td>LN</td>
<td>Large, irregular, bleeding</td>
</tr>
<tr>
<td>Comments</td>
<td>Rare in US, except MSM</td>
</tr>
</tbody>
</table>

Evaluation of the Patient with Genital Ulcer

- A diagnosis based on history/physical is often inaccurate
- Obtain a serologic test for syphilis
  - When available: dark-field microscopy (70-90% sensitivity) or DFA
  - If serology negative, repeat at 1 & 3 months
- Culture (or antigen test) for herpes simplex
- In endemic areas or during outbreak: GS/Culture of edge of ulcer for H. ducreyi (53-88% sensitive)
- MSM and endemic areas: serology for LGV and Chlamydia PCR / NAAT
- Consider empiric therapy based on most likely diagnosis

Chlamydia trachomatis species causing Human Disease

<table>
<thead>
<tr>
<th>Serovar</th>
<th>Associated syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-C</td>
<td>Conjunctivitis (Trachoma)</td>
</tr>
<tr>
<td>D-K</td>
<td>NGU, mucupurulent cervicitis, PID, neonatal conjunctivitis</td>
</tr>
<tr>
<td>L1, L2, L3</td>
<td>Lymphogranuloma venereum</td>
</tr>
</tbody>
</table>

LGV Emerging Epidemiology

- Clusters of cases of lymphogranuloma venereum proctitis, have been described in men who have sex with men in urban centers
- The dominant seovar was C. trachomatis serovar 2
**LGV**

- **Primary lesions** (3-30d incubation): papule of small ulcer, indistinct from HSV or syphilis, often painless
- **Secondary stage** (2-6w)
  - Anogenitorectal: proctitis (purulent, mucous, bloody)
  - Inguinal: buboes, cellulitis, periadnitis, dissemination
- **Long-term complications**: chronic ulceration, fistulae, strictures, genital elephantiasis
- **Diagnosis**
  - **Culture**: positive in <30% of cases
  - **Nucleic acid testing**: may be positive in early stages, not FDA approved, and requires lab validation
  - **Serology**: complement fixation (CF ≥ 1:64) or microimmunofluorescence (MIF ≥ 1:128)

**Clinical Manifestations of LGV**

- **Primary Lesion**
- **Secondary Stage**
  - Proctitis and cellulitis

**Complications**

- **Anal Stricture**
LGV Therapy

- Treat suspected cases, as diagnosis is challenging
- Treatment:
  - doxycycline, 100 mg BID x 21 days
  - alternative: azithromycin 1g/week x 3 weeks
- Asymptomatic sex partners:
  - doxycycline 100 mg bid x 7 days
  - azithromycin 1g x1

Syphilis

After declining every year since 1990, the number of reported cases of early syphilis in the US have been consistently rising since 2001.

Outbreaks among men who have sex with men (MSM), many of them co-infected with HIV, are responsible for the observed rise, but recent increase has been seen in women as well.

Syphilis-Stages

- Primary: Incubation: 3-90 days, painless chancre (begins as papule), heals spontaneously in 1-8 weeks
- Secondary: 2-8 weeks after primary but chancre may still be present; Systemic SXs common
- Latent
- Tertiary
  - Cardiovascular
  - Gumma
  - Neurological

Primary and Secondary Syphilis, U.S., 2009

<table>
<thead>
<tr>
<th>Cases</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cases</th>
<th>Male</th>
<th>Female</th>
<th>MSM†</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,000</td>
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<td></td>
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<tr>
<td>2,000</td>
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<td></td>
<td></td>
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<tr>
<td>3,000</td>
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<td></td>
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<tr>
<td>4,000</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,000</td>
<td></td>
<td></td>
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</tbody>
</table>

Syphilitic Rash

- Lesions usually begin on the trunk and proximal extremities
- They are bilateral, pink to red, discrete macules but may turn pustular
- Any surface area of the body can become involved
- Although lesions on the palms and soles strongly suggest the diagnosis they are NOT the most common ones

Syphilitic Rash

- Lesions usually begin on the trunk and proximal extremities
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- Any surface area of the body can become involved
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Syphilitic Condylomata Lata, Male

Syphilitis Condylomata Lata, female

Primary HIV

Diagnostic Tests for Syphilis

- Direct identification (darkfield, DFA) = most definitive
- Nontreponemal tests
  - Venereal Disease Research Lab (VDRL) or Rapid Plasma Reagin (RPR) are used as a screening tool
  - Prozone phenomena (2%) – dilute the RPR
  - RPR titers are used to follow response to therapy
- “Traditional” Treponemal tests
  - FTA-abs, MHA-TP/TPHA, and TPI
  - Specific, but more labor intensive
  - Used to confirm infection
  - Will remain positive for life in >90%
- Novel serologic tests: EIA, WB (more sensitive in early disease?), PCR

Syphilis Serology Sensitivities

<table>
<thead>
<tr>
<th>Test</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDRL</td>
<td>70%</td>
<td>99%</td>
<td>56%</td>
</tr>
<tr>
<td>RPR</td>
<td>80%</td>
<td>99%</td>
<td>56%</td>
</tr>
<tr>
<td>FTA-abs</td>
<td>85%</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>MHA-TP/TPHA</td>
<td>65%</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>TPI</td>
<td>50%</td>
<td>97%</td>
<td>95%</td>
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</tbody>
</table>

Novel Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sena et al. CID; 2010: 51: 707-710</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTIA</td>
<td>98.2%</td>
</tr>
<tr>
<td>VDRL</td>
<td>80.2%</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>100%</td>
</tr>
</tbody>
</table>
The Prozone reaction

False Negative Syphilis Screening Tests

- The RPR testing methodology uses charcoal particles, added to a cardiolipin Ag suspension
- A test is positive when an optimal Ab:Ag ratio creates a precipitate (lattice, also referred to as the zone of equivalence). Charcoal is trapped in this lattice and allows the reaction to be visible macroscopically
- Antibody excess (prozone) or antigen excess (postzone) will yield false negative test results because they do not form the lattice needed to trap the charcoal particles

Syphilis

Follow Response to Treatment

- Re-examine clinically and follow non-treponemal test titer (RPR, VDRL)
- Goal: sustained ≥ 4-fold decrease in titer and symptom resolution
- Testing intervals:
  - Primary/secondary syphilis: 6 and 12 months
  - Late syphilis: 6, 12, 18, and 24 months
  - HIV-infection: 3, 6, 9, 12, and 24 months (most respond to therapy)

Syphilis

Treatment Failure

- Definition of treatment failure:
  - Signs/symptoms persist
  - Failed to achieve 4-fold decrease in titer within 6-12 months
  - Sustained 4-fold increase in titer (e.g. 1:8→1:32; repeat 1:32)
- Management of treatment failure:
  - HIV test (should have been done at diagnosis)
  - CSF analysis
  - If CSF normal administer benzathine pcn weekly x 3 wks
  - If titers don’t decline after repeat therapy (re-infection not suspected and the CSF examination is normal) no additional therapy indicated

Neurosyphilis

- May occur during any stage
- Indication for CSF Analysis
  - Symptoms: asymptomatic, meningitis, cranial nerve palsies, general paresis, tabes dorsalis, meningovascular disease, auditory symptoms, optic neuritis, cognitive dysfunction,
  - CSF-VDRL is specific but insensitive
  - Elevated CSF protein and WBC (>4/mL) is supportive but non-specific.
  - >20cells/mL may be more specific in HIV-infected
- CSF should be followed after treatment until normal (6m, 2y)
- When in doubt consider empiric therapy

Ulcerative Diseases - Herpes

- Herpes, herpes, herpes: In the US atypical presentations of genital herpes are far more common than all other genital ulcers combined
- Classic presentation: cluster of small painful vesicular lesions – present in 60-70% of clinically symptomatic cases but absent in most infected individuals
- Other presentations: asymptomatic infection, ulcerative lesions, fissures cervicitis, proctitis (rectal pain, tenesmus), urethritis, erythema multiform, recurrent meningitis, hepatitis

Categories of Genital Herpes Infections

- Primary first-episode
- Non primary first-episode
- Recurrent
- Asymptomatic Shedding
Genital HSV - Epidemiology
- At least 50 million persons, 12 and older, in the US are infected with HSV-2.
- HSV-2 is more common in women (~25%) than men.
- Most (as many as 90%) of HSV-2-infected individuals are undiagnosed and unaware of their infection; those periodically shed virus in their genital tract (2-28% of days).
- Most transmission is from asymptomatic carriers.
- 5-50% of clinical genital HSV is caused by HSV-1.
- Recurrence and asymptomatic shedding are more common with genital HSV-2.

HSV-2 – Diagnostic tests
- Culture, then typing by DFA (HSV1 or HSV2) (24-72h)
- Higher sensitivity with primary infection.
- Sensitivity in recurrent disease is only 40-70%.
- Isolation rates are higher for early lesions.
- Tzanck smear (Giemsa Stain) – 60% sensitive.
- DFA - detection of viral Ag from a lesion (several hours).
- PCR assays with improved sensitivity may soon replace standard viral isolation culture; not approved for testing genital secretions (often used for CSF evaluation).
- Type-specific Serology.

Type-Specific HSV-2 serology
- Testing for antibodies directed against HSV type-specific glycoproteins (GP-G1 & G2 for HSV 1 or 2).
- Sensitivity 80-98%, Specificity > 96%.
- Point-of-care tests are available.
- Evolving role in clinical practice: assessment of partners, diagnosis of culture-negative ulcers, STD screen, identification of asymptomatic carriers, vaccine candidates.
- Limitations: lag after initial exposure, a positive test only indicates previous exposure.

Genital HSV Prevention

Antiviral Therapy for Prevention of HSV-2 Transmission
- Prospective placebo-controlled study of heterosexual HSV-2 sero-discordant couples.
- HSV-2 positive partner given valacyclovir 500 mg daily or placebo.
- HSV-2 susceptible partners assessed monthly.
- Condoms and safe sex counseling provided at all visits.
- After 8 months of therapy Symptomatic HSV-2 transmission was reduced by 77%, and asymptomatic acquisition by 50%.
- Valacyclovir is now FDA approved for this indication.

Chancroid
- Caused by Hemophilus ducreyi.
- Very rare in the US.
- Presents as painful ulcer with irregular edges and regional lymphadenopathy.
- Diagnosis by gram stain (typical) or culture on special media.
- Treatment:
  - Azithromycin 1 g x one dose
  - Ceftriaxone 250 mg IM x 1 dose
  - Ciprofloxacin 500 mg PO BID x 3 days
  - Erythromycin 500 mg PO QID x 7 days.

Chancroid Male
Kissing Ulcers and regional lymphadenopathy.
Non-Ulcerative Sexually Transmitted Diseases

Clinical Manifestations of Gonorrhea

- Urethritis (men or women)
- Epididymitis
- Cervicitis
- PID
- Proctitis
- Pharyngitis
- Disseminated infection (DGI) (complement deficiency, women > men, tenosynovitis, dermatitis)
- Conjunctivitis
- Rare: meningitis, hepatitis, endocarditis

Diagnosing Gonorrhea

- Gram stains: 95-100% sensitive 98% specific in male urethritis; o/w low sensitivity
- Culture: for sites not approved for NAAT (rectal, pharyngeal) or if susceptibility testing required, 35-37°C, 3-5% CO₂, Thayer-Martin
- Nucleic acid amplification tests (NAATs) approved for vaginal, endocervical, urethral & urine specimen; 97-99% sensitive and 99% specific for cervical & urethral swabs. Some labs validated for oral and rectal; not FDA cleared

Cipro-resistant Gonorrhoeae Rates

Gonococcal Isolate Surveillance Project (GISP)

Cipro-resistant rates have shown an increase over the years. In 1990, the rates were 0.9% for penicillin-resistant (PenR) and 3.8% for quinolone-resistant (QRNG). By 2009, the rates had increased to 2.1% for PenR and 7.9% for QRNG. The resistance to these antibiotics is becoming a major concern in the treatment of gonorrhea.

Gonococcal Isolate Surveillance Project (GISP)—Penicillin, Tetracycline, and Ciprofloxacin Resistance Among GISP Isolates, 2009

- QRNG 24% in MSM, 3.6% in MSW
- Use of FQ is NOT recommended unless susceptibility results available
- Antimicrobial susceptibility results only available with culture tests
- Perform culture & susceptibility if GC infection persists or recurs
- Most common cause is re-infection
- True Rx failures or resistant GC isolates should be reported

The Boston Globe

The Boston Globe's article discusses the increase in quinolone-resistant gonorrhea isolates in Massachusetts.

The1998 study revealed a 1.2% quinolone-resistant rate, whereas the 2009 study showed a 7.9% rate. This significant increase highlights the need for better antibiotic usage and susceptibility testing to manage the spread of resistant strains.
**Treatment of Gonorrhea**

- IM ceftriaxone (250 mg) is the treatment of choice (PO cefixime 400 mg orally is an alternative); cefuroxime not adequate
- Plus treatment for Chlamydia
- True beta-lactam allergy:
  - Spectinomycin 2 g IM (no longer available in the US) plus Chlamydia therapy or
  - Azithromycin 2 g po x1 dose (some resistance reported)
- Although all isolates are currently susceptible, a recent shift towards higher ceftriaxone MICs (hence 250mg dose)
- Higher dose for DGI
- Rescreen at 3m or within 12m (NOT A TEST OF CURE)

**Epidemiology of Chlamydia trachomatis (serotypes D-K)**

- Most frequently reported infectious disease in the US
- At least 75% of women and 50% of men have no symptoms
- Rapid diagnostic tests allow for easier office testing and self-sampling / home-testing (latter not yet approved in US)

**Chlamydia, United States, 2009**

<table>
<thead>
<tr>
<th>Men</th>
<th>Rate (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>7.7</td>
</tr>
<tr>
<td>16-19</td>
<td>10.6</td>
</tr>
<tr>
<td>17-19</td>
<td>12.5</td>
</tr>
</tbody>
</table>

**Screening for Chlamydia trachomatis**

- Up to 40% of women with untreated chlamydia will develop PID. Of those with PID:
  - 20% will become infertile
  - 18% will experience chronic pelvic pain
  - 9% will have a tubal pregnancy
- Two CDC asymptomatic screening studies have resulted in decline in overall infection rates
- Chlamydia screening followed by treatment not only reduced the prevalence of lower genital tract infection, but also complication rates and cost

**Screening for Women (risk based), MA DPH:**

- <20 y/o with every pelvic exam and at least once a year
- 20-24 at least once a year
- >24 screen at least once a year if at risk:
  - inconsistent use of barrier method
  - new or more than one partner in last 3 months
  - other STD
- Screening for Men: no routine screening. May be considered in high risk setting (adolescent and STD clinics, correctional facilities)

**Chlamydia Rescreening and test-of-cure**

- CDC guidelines: rescreen all women with Chlamydia infection 3-4 months after treatment or when they next present for care
- Rescreening is distinct from early retesting to detect therapeutic failure (test-of-cure)
- Except in pregnant women, test-of-cure is not recommended unless therapeutic compliance is in question
In 2006, a genetic variant of *Chlamydia trachomatis* not detectable with some commonly used diagnostic tests was identified in Sweden.

- US rates not known
- Has a 377 base pair deletion in the cryptic plasmid
- 23% of all Chlamydia cases diagnosed
- 29% in age group 20-29
- Will not detect variant: Roche Cobas Amplicor, PCR/TaqMan 48, Abbott Real Time CT
- Will detect variant: GenProbe Aptima targets 16SrRNA gene, Artus-Real Art CT-PCR targets the MOMP-1gene; Becton Dickinson-Probe Tec

**Screening for GC and Chlamydia Using NAAT**

1,110 MSM in a San Francisco STD clinic, rates of infection using culture and NAAT. NAAT detected twice as many infections as culture.

**New Screening Guidelines for MSM**

- HIV test if not done in the past year
- Syphilis serology with confirmatory testing
- Urethral or urinary GC and Chlamydia (if insertive)
- Rectal GC and Chlamydia (NAAT preferred, if receptive)
- Pharyngeal GC (NAAT preferred, if receptive oral)
- Consider serologic evaluation for HSV-2
- HBsAg
- HCV if also using drugs (receptive anal? not in guidelines)
- Vaccines for HAV and HBV
- Screen q3-6m if multiple anonymous partners

**Question 1**

A pregnant woman is referred for a lab finding of an RPR titer of 1:8 and a positive FTA during her first prenatal visit. She reports no h/o syphilis, and is asymptomatic. She reports an allergy to beta-lactam antibiotics (hives during a course each of of amoxicillin and cephalexin). What is the most appropriate treatment?

**What is the most appropriate treatment?**

- a. This is a false positive test due to pregnancy, no treatment recommended
- b. Doxycycline 100 mg orally bid, for 14 days
- c. Doxycycline 100 mg orally bid, for 28 days
- d. Azithromycin 2g in a single dose
- e. Desensitization, and treatment with penicillin
**Question 2**

A 57 y/o MSM with allergies to beta-lactams and azithromycin is seen for a penile discharge and dysuria. NAAT is positive for both GC and Chlamydia. He receives a dose of ciprofloxacin (500mg) and a one week treatment course of doxycycline. He returns to urgent care at the end of the treatment course reporting no improvement. A probe is repeated and is again positive for both organisms. Which of the following statements is incorrect?

- Re-infection is a common cause of relapsed symptoms
- One week is too early for a test of cure (repeat probes)
- FQ-resistant gonorrhea should be suspected and culture and sensitivities are recommended
- FQ-resistant Chlamydia should be suspected, culture is recommended, and azithromycin should be prescribed

**Syphilis in Pregnancy**

- Screen in first prenatal visit
- Screen high risk mothers again around 28 weeks and at delivery
- Treat for appropriate stage of syphilis (although some expert endorse additional doses for early syphilis)
- Treat with penicillin, even if desensitization required
- Repeat RPR titer at 3 months

**What is the most appropriate treatment?**

- a. This is a false positive test due to pregnancy, no treatment recommended
- b. Doxycycline 100 mg orally bid, for 14 days
- c. Doxycycline 100 mg orally bid, for 28 days
- d. Azithromycin 2g in a single dose
- e. Desensitization, and treatment with penicillin

**Question 2**

Which of these statements is incorrect?

Correct answer (incorrect statement) is d

- a. Re-infection is a common cause of relapsed symptoms
- b. One week is too early for a test of cure (repeat probes)
- c. FQ-resistant gonorrhea should be suspected and culture and sensitivities are recommended
- d. FQ-resistant Chlamydia should be suspected, culture is recommended, and azithromycin should be prescribed