Sexually Transmitted Bacterial Infections
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Dr. Rein has no conflicts of interest to declare

Why are STDs STDs?

- Limited environmental survival of the pathogens
- Limited sites of infection
- Lesions of disease, containing large numbers of organisms, tend to be in the genitals
- Expanded definition of sexual practices
- Expanded definition of sites used for sex

Limited Sites of Infection: an example

- Anatomic sites in adults which can be infected with the gonococcus and chlamydia
  - Urethra
  - Cervix (not vagina in adults)
  - Throat (not mouth)
  - Rectum
  - Eye

Oral sex is common

- National Survey of Family Growth, 2007-2010, ages 15-24, 3242 women, 3140 men

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>78%</td>
<td>75%</td>
</tr>
<tr>
<td>Ever had oral sex</td>
<td>66%</td>
<td>65%</td>
</tr>
<tr>
<td>Timing vs first vaginal intercourse:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Simultaneous</td>
<td>7.4%</td>
<td>12%</td>
</tr>
<tr>
<td>After</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>Never had vaginal intercourse</td>
<td>5.4%</td>
<td>6.5%</td>
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</tbody>
</table>

Questions regarding oral sex should be part of the sexual history

Anal sex is common

- National Survey of Family Growth
- 12,571 men and women age 15-44 years
- ⅓ have had anal sex at least once

Therefore, questions regarding anal should be part of the sexual history


Recognizing a disease as sexually transmitted allows one to:

- Recognize that there is always more than one person who needs attention
  - “Source” or “spread” cases
- Identify a population at high risk for the infection: the population of sexual partners
  - Epidemiological treatment
- Identify persons at higher risk for other STD
  - Understanding coprevalence absolutely critical
  - Advise HIV testing
- Increase cure rates by treating partners “simultaneously”
  - Before additional sexual contact
  - Consider expedited partner therapy

Rectal GC/CT a marker for HIV

- 3370 MSM @ NYC public STD clinics
  - Rectal GC: 109 cases, 72% asymptomatic
  - Rectal CT: 226 cases, 85% asymptomatic
- Prospective followup: ~938 person-years
- Annual incidence of HIV %:
  - CT + (177) 5.9 (3.6-9.1)
  - GC+ (69) 7.1 (3.3-14)
  - GC and CT + (30) 10.7 (3.9-24)
  - None 2.5 (1.3-1.4)


Coprevalence again

- iPrEx study
  - 2499 HIV- men and transgender women
  - 333 initially syphilis seropositive
- Incident syphilis
  - 7.3 cases/100 person-years
  - HIV incidence:
    - No syphilis: 2.8 cases/100 person-years
    - Syphilis: 8.0 cases/100 person-years
    - Hazard ratio 2.6 (1.6-4.4), P<.001
- If syphilis present in MSM encourage HIV testing and consider recommending pre-exposure prophylaxis

Solomon MM et al: Clin Infect Dis 2014; epub
Coprevalence - STI in an Neapolitan Renaissance Mummy

- Maria d’Aragona, Marquise of Vasto (1503-1568)
- Cutaneous ulcer
  - Indirect immunofluorescence: filaments resembling treponemes
  - Electron microscopy: typical spirochetes with axial filaments
- Exophytic inguinal lesion
  - Light microscopy: parakeracytosis
  - Molecular studies: HPV 18 (100% similarity of sequences)
- Fornaciari: Med Secoli 2006;18:843-64

But recognizing a disease as sexually transmitted

- Invokes a dramatic stigmatization that can interfere with control strategies
- Increases challenges in treating individual patients
- Indicates that some (many) cases can be prevented by changes in behavior
  - Attempts to modify sexual behavior have not been very successful
  - Merely educating the public about the medical risks of STD doesn’t seem to work

STD Results Viewable On-Line

- Send anonymous notification to partners
- Don’t Spread It
- In SPOT
- So They Can Know
- Let people check in
- Hula (mobile app)
  - "Helps you get laid"
  - "Friend" can see data
- Chexart, CheckMate: allow posting of results to subscribers
- The problem with time-sensitivity (OMG)

The emancipated minor

Virginia code § 54.1-2969

- A minor shall be deemed an adult for the purpose of consenting to medical or health service needed to:
  - Diagnose or treat venereal (or any reportable)disease
  - Manage birth control, pregnancy, or family planning (not sterilization)
  - Accessing or authorizing disclosure of medical records
Should clinicians be concerned about STI among seniors?

- Yes:
  - Pregnancy not an issue so less condom use
  - Senior residences are "like college dorms"
  - New drugs

- Increases in STI 2007-2011

<table>
<thead>
<tr>
<th>Age Group</th>
<th>≥65 Years</th>
<th>20-24 Years</th>
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</thead>
<tbody>
<tr>
<td>Chlamydia Infx</td>
<td>31%</td>
<td>35%</td>
</tr>
<tr>
<td>Syphilis</td>
<td>52%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Emanuel EJ: NY Times 2014; January 18 Sunday Review

#### Urethritis

- Inflammation of the urethra
- Men: Some combination of discharge and dysuria
- Women:
  - Discharge often missed
  - Presents as internal dysuria (external dysuria suggests vulvovaginitis)

#### Differentiating GCU from NGU

- Quite unreliable
  - History
  - Physical Examination
- Often not available
  - Gram stain
  - Cultures
- Nucleic Acid Amplification Tests
Clinical features of Gonococcal and Nongonococcal Urethritis

<table>
<thead>
<tr>
<th>Incubation period</th>
<th>Gonococcal</th>
<th>Nongonococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Subacute</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Prominent</td>
<td>Milder</td>
</tr>
<tr>
<td>Dysuria alone</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Discharge alone</td>
<td>27%</td>
<td>47%</td>
</tr>
<tr>
<td>Both</td>
<td>71%</td>
<td>38%</td>
</tr>
<tr>
<td>Discharge character</td>
<td>Purulent</td>
<td>Mucopurulent</td>
</tr>
</tbody>
</table>

Can't reliably tell GC and NGU apart clinically
Milder symptoms may delay seeking medical attention. This is especially true for the medically disenfranchised.

The Gram stain is nice, but:
- Starving pathologists have enacted legislation that presents many of us from doing it.
- Once you have made a diagnosis of gonorrhea by Gram stain you can no longer confirm or rule out coincident infection with an agent of NGU
- So, if one has diagnosed GCU in this manner, one should also treat for coincident NGU
- More on this later

Key points
- NGU is a syndrome with multiple etiologies
  - *Chlamydia trachomatis* is not the only cause
  - *Mycoplasma genitalium* is an important etiology
  - Sexual contacts to NGU should be epidemiologically treated even if chlamydia negative
- Always treat gonorrhea with two drugs
  - Provides double coverage for GC
  - Treats coincident nonchlamydial NGU

Nongonococcal Urethritis
- A syndrome with multiple causes
- Epidemiological treatment is important
- Don't rely too much on chlamydial tests
- *Mycoplasma genitalium* is a newly recognized and important pathogen
NGU: Clinical features

- Discharge 55%
- Dysuria 5%
- Discharge and dysuria 40%


The so-called urethral syndrome

- Symptoms: dysuria, frequency
- Laboratory: pyuria, “sterile” cultures
- Differential diagnosis:
  - Low level bacteriuria
  - Gram-negative urethritis
  - Nongonococcal urethritis
  - Beware of recurrent, culture-negative urinary tract infection

Etiologies of NGU

- *Chlamydia trachomatis* 25%
- *Mycoplasma genitalium* 10%-25%
- *Ureaplasma urealyticum* 16-26%
- *Trichomonas vaginalis* ~1%
- Herpes simplex
- Enterobacteriaceae
- “Ideopathic” (so far)
Mycoplasmas in NGU
- STD Clinic: 238 with NGU, 237 Controls
- Multiplex PCR
- Odds ratio of NGU associated with:
  - *C. trachomatis* 7.5 (P < 0.001)
  - *M. genitalium* 5.5 (P = 0.027)
  - *U. urealyticum* 2.0 (P = 0.04)
- These organisms are independently associated with NGU.

*M. genitalium* as a cause of NGU
- Median prevalence among men with nonchlamydial NGU = 25% (10%-38%)
- Prevalence vs asymptomatic control group
  - Statistically significant in 16/22 studies (73%)
  - Odds ratios: 2.2 - 20.3
- Dose-response relationship to severity
- Clinical resolution associated with elimination of organism

*M. genitalium* among MSM
- British SDT Clinic
  - Urine specimen: 6.6%
    - Associated with dysuria
  - Rectal: 4.4%
    - Asymptomatic
    - Carriage associated with HIV positivity
      - P < 0.001
doi:10.1136/sti.2009.038190, October

*Mycoplasma genitalium* in women
- Cervicitis
- Endometritis
- Salpingitis
- Asymptomatic carriage
  - Sweden: 6%
  - US STD Clinics: 7%
  - Britain, pregnant: 0.7%
**M. genitalium** in cervicitis

- Data weak because of differing definitions of cervicitis (clinical vs presence of PMN)
- 8/14 (57%) of studies showed significant association
  - Odds ratios 1.2 – 5.7
  - Inadequately adjusted for other factors


**M. genitalium** in PID

- Culture:
  - Odds ratio 4.6 – 6.3
  - One case report: detected in Fallopian tubes
- 157 women with acute PID
  - *M. genitalium* isolated from 28 (18%)
  - Histologically proven acute PID
  - *M. genitalium* isolated from 28 (18%)
  - If *M. genitalium* present, risk increased ~4X
  - Not covered by standard regimen of a cephalosporin, doxycycline, and metronidazole


**M. genitalium** in GYN disease

- Sweden, GYN outpatient clinic
- *M. genitalium* vs uninfected controls
  - Cervicitis: 22.3% (21/94) P < .001
  - PID: 4.9% (4/81) P < .013
- *C. trachomatis* vs uninfected controls
  - Cervicitis: 18.3% (20/109) P < .001
  - PID: 4.9% (4/81) P < .001
- Negative controls: PID: 346, Cx: 429


Nomarski microscopy (x100 objective) of sperm incubated in vitro with *M. genitalium*

A scenario I sometimes encounter:

- Man diagnosed with NGU on the basis of finding inflammatory cells in his penis
- Female partner goes to her physician and has a NAAT for *Chlamydia trachomatis*
- She is told told: “You don’t have chlamydia, so you don’t need treatment.”
  - “You couldn’t have given this to him. He must be having sex with someone else”
- Is this approach correct?????

Epidemiological Treatment of Nongonococcal Urethritis

- Male NGU may be diagnosed by the presence of urethral inflammation which is independent of etiology.
- A female contact to a man with NGU may not be infected with *Chlamydia trachomatis* but rather with one of the other agents:
  - *Ureaplasma urealyticum*
  - *Mycoplasma genitalium*
  - *Trichomonas vaginalis*
- Therefore: Such female contacts should be treated even if they are negative for *Chlamydia trachomatis*.

Rx of Chlamydial NGU: Meta-analysis

- 23 studies: 1147 Rx azithromycin, 912 RX doxycycline
- All cases:
  - Fixed effect pool: efficacy difference 2.6% (0.5-4.7)
  - Azithromycin: 96.2% (94.9-97.5)
  - Doxycycline: 97.4% (96.2-98.7)
- Things to consider:
  - More pronounced among patients with higher organism loads
  - Difference increased since 2002
  - Most not double-blind
  - Could not get drug company data
  - Difference disappears when several small studies excluded
  - Followup bias?
  - These were studies (informed consent)

Treatment of *M. genitalium* urethritis

- Microbiological cures, pooled data
- Doxycycline 100 mg twice daily for 7-8 days
  - Cured 88/212 (42%) of men
- Azithromycin, 1 gm
  - Cured 371/466 (80%) of men
- Longer courses of azithromycin: no demonstrated advantage


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Application

- Single-dose azithromycin probably superior to doxycycline overall in NGU
- Compliance is very important

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*M. genitalium* induced resistance to macrolides

- 15 patients infected with *M. genitalium*
  - Pretreatment isolates sensitive to azithromycin
  - Failed treatment with azithromycin
  - Persistent infection
    - Organisms now resistant to azithromycin
    - Sensitive to moxifloxacin but not some older fluoroquinolones
  - Cured with moxifloxacin 400 mg daily by mouth for 10 days


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Azithro/Moxi resistance in *M. genitalium*

- 143 Australian STD Clinic patients: PCR-positive for *M. genitalium*
  - 23S rRNA: Azithromycin resistance 43%
  - ParC and GyrA: Moxifloxacin resistance 15%
- 33 pts with known clinical course: Mutations correlate with failure
  - Azithromycin resistance:
    - Clinical failure: p = .024
    - Microbiological failure: p = 0.013
  - Moxifloxacin resistance:
    - Combined failure: p = 0.005

Empirical approach to NGU treatment failures

- Tetracycline/Doxycycline failure:
  - Metronidazole/Tinidazole for trichomoniasis
  - Azithromycin for mycoplasmas

- Azithromycin failure:
  - Metronidazole/Tinidazole for trichomoniasis
  - Moxifloxacin 400 mg orally daily for 10 days
    - Also covers C. trachomatis
    - Not FDA approved


Retreatment of *M. genitalium*

- Microbiologic failures after second treatment:
  - Doxycycline ⇀ Azithromycin 29%
  - Azithromycin ⇀ Doxycycline 70%

- Microbiologic failures after subsequent treatment with moxifloxacin: 12%-15%


We should treat all gonorrhea cases for coincident NGU

- Patients with gonorrhea may be carrying one of the other causes of NGU, like *M. genitalium*
- Use dual therapy even if negative for C. trachomatis
- If you don’t use dual therapy:
  - Beware of postgonococcal urethritis
  - Patient treated for gonococcal urethritis with β-lactam
  - Partial response or response with relapse in absence of reexposure
  - Treat for agent of NGU
- Treat partners as well
- Dose of azithromycin – see below (2012 GC recs)!

Key Points

- *Neisseria* gonorrhoeae has become resistant to most drugs used to treat it
- Resistance most pronounced in West and among MSM (this is where it starts)
- Always treat gonorrhea with two drugs
  - Provides double coverage for GC
  - Treats coincident nonchlamydial NGU
- Expedited partner therapy is supported by many groups but should not be one’s first approach
  - May be only minimally effective in absolute terms
  - Raises ethical (and perhaps some legal) issues
Gonococcal cephalosporin resistance

- Combined effects of several chromosomal mutations
- Oral cephalosporin resistance documented in the U.S. MICs increasing to injectable cephalosporins
- Oral and injectable cephalosporin resistance documented in the Far East and Europe

Gonococcal resistance 2012 GISP

- Gonococcal Isolate Surveillance Project (GISP)
- National sample, 34,800 urethral isolates
- Resistance phenotype
  - MSM
  - MSW
  - Azithromycin: ~8K 0.9% 0.2%
  - Cefixime: 1.7% 0.2%
  - Ceftriaxone: 0.4% 0.1%
  - Ciprofloxacin: 29.9% 6.9%
  - Tetracycline: 37.4% 13.2%
  - "Multidrug": 0.8% 0.1%
- Each significant at p < 0.001


Gonococcal resistance in MSM

- Gonococcal Isolate Surveillance Project (GISP)
- National sample, 34,800 urethral isolates

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<tr>
<th>Resistance phenotype</th>
<th>MSM~8K</th>
<th>MSW~26K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>0.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cefixime</td>
<td>1.7%</td>
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</tr>
<tr>
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</tr>
<tr>
<td>&quot;Multidrug&quot;</td>
<td>0.8%</td>
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</tbody>
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Each significant at p < 0.001


Azithromycin-resistant GC

- Hawaii, 5/17/11: MIC 1024 μg/mL
- San Diego, Aug-Oct, 2009
  - 5 cases, MSM, not linked
  - Symptomatic urethritis
  - MIC: 8-16 μg/mL
  - Susceptible: penicillin(!), cephalosporins, fluoroquinolones, tetracyclines
- San Diego, Nov 2009 – December 2010
  - 4/229 (1.7%) of isolates
  - MIC: 8-16 μg/mL
Recommended GC regimens (for now)

- Ceftriaxone 250 mg im plus azithromycin 1 gm po
- Don’t use ciprofloxacin
- Don’t use cefixime (but wait, what about expedited patient therapy?)

Could ceftriaxone use actually decrease cure rates??

- Mathematical model (remember GIGO)
- Assumptions
  - Decreased cefixime susceptibility in 2% of heterosexuals and 5% of MSM
  - Oral Rx failure in 10% of cases with decreased susceptibility
  - Oral Rx given to 30% of heterosexual and 15% of MSM
  - Expedited partner therapy (EPT) in 30% of heterosexuals
- Results: decreased cure rates if:
  - 5% of index cases don’t get treated
  - EPT eliminated
  - EPT used but only 75% effective

Golden MR, Sex Transm Dis 2014;41:619-25

GC Treatment failures

- If treated with second-line regimen:
  - Ceftriaxone 250 mg im + azithromycin 2 gm
  - Make sure sexual partners are treated with same regimen
- If treated with standard, first-line regimen:
  - Careful, complete sexual history (including geography) to insure that this is not reinfection
  - Culture organism, so sensitivity testing can be done
  - Call an expert

Future treatments for resistant gonorrhea

- CDC/NIH study: heterosexual men and women and MSM
  - 240 mg gentamicin IM + 2 gm azithromycin po
    - Cured 202/202 (≥98.5%) anogenital infections
    - Cured 10/10 pharyngeal infections
  - 320 mg gemafloxacin po + 2 gm azithromycin po
    - Cured 198/199 (≥97.6%) anogenital infections
    - Cured 15/15 pharyngeal infections
- Lots of GI side effects, not FDA approved

Kirkcaldy RD et al: CDC Webinar July 21, 2011
ISSTDR/ISASTDI

Golden MR, Sex Transm Dis 2014;41:619-25
Rx of Pharyngeal GC (retrospective)

- 1993-2011, 90% asymptomatic.
- Positive test 7-180 days after initial Rx. 1440 cases, 84% MSM
- Combination therapy: failure rates
  - Oral cephalosporin + azithromycin 7.0%
  - Cefpodoxime + azithromycin 7.7%
  - Cefixime + azithromycin 6.0%
  - Ceftriaxone + azithromycin 11.3%
- Single drug RX
  - Ceftriaxone 9.1%
  - Cefixime 20.8%
  - Cefpodoxime 33.4%


Transmission from Oropharynx to Penis

- San Francisco STD Clinic, MSM, insertive fellatio only in 3 months
- Chlamydia trachomatis N = 397
  - 4.8% Ct positive
    - HIV positive 16.0%
    - HIV negative 3.0%
- Neisseria gonorrhoeae N = 395
  - 4.1% GC positive
    - HIV positive 10.0%
    - HIV negative 3.0%


USPSTF recommendations for screening of asymptomatic patients

- Use nucleic acid amplification tests
- Chlamydia: nonpregnant women
  - Sexually active ≤ 24 yo
  - Older at increased risk for infection
  - No support for screening men
- Gonorrhea
  - Sexually active ≤ 24 yo
  - Older at increased risk for infection
  - No support for screening men


USPSTF recommendations for screening of asymptomatic patients

- Such screening in women “moderately” reduces incidence of PID
- No data supporting reduction in transmission or complications by screening men
- “Moderate certainty”

Additional CDC recommendations for GC/Ct screening

- Rescreen all women treated for gonorrhea or chlamydial infection at 3 months after treatment regardless of whether or not they feel that partner(s) have been treated.
- Annually (or more frequently) MSM based on exposure history
- GC: high-risk pregnant women, Ct: all pregnant women

NYC: Syphilis in MSM vs MSW

- Denominator: Population based surveys 2005-2008
- Numerator: Syphilis diagnosis from surveillance registries
- Same sex contact
  - NonHispanic black men: 2.3%
  - NonHispanic white men: 7.4%
- Condom use at last sex:
  - MSM: 62.9%
  - MSW: 38.3%
- Newly diagnosed syphilis in MSM:
  - 707/100K, 140X rate in MSW

Pathela P et al: JAIDS 2011;58:408-16

Coprevalence again

- iPrEx study
  - 2499 HIV- men and transgender women
  - 333 initially syphilis seropositive
- Incident syphilis
  - 7.3 cases/100 person-years
- HIV incidence:
  - No syphilis: 2.8 cases/100 person-years
  - Syphilis: 8.0 cases/100 person-years
  - Hazard ratio 2.6 (1.6-4.4). P<.001
- If syphilis present in MSM encourage HIV testing and consider recommending pre-exposure prophylaxis

Solomon MM et al: Clin Infect Dis 2014; epub

Important Intervals in Syphilis

- Critical Period = 90 days
  - AKA: maximum estimate of incubation period
  - Theoretical maximum time before development of clinical or serological evidence of syphilis
  - Patients with contact to lesion syphilis in past 90 days should receive epidemiological treatment
- Early latency: 1 year
  - Time during which 25% suffer mucocutaneous relapse (MR) and again become contagious
  - 90% of MR in first year, 4% in year two
  - Contact history probably important

Remember:

- Oral sex is important in the epidemiology of syphilis (and other STD)
- The only sexually transmitted condition that cannot be acquired through oral sex is "pregnant"
- Take a complete sexual history, which includes oral sex

Syphilis acquired through oral sex

- Chicago, 2000-2002, data available on 627/962 cases of P&S syphilis
- 13.7% of cases occurred in people whose only exposure was fellatio or cunnilingus
- These cases accounted for:
  - 20.3% of cases among MSM
  - 6.4% of cases among heterosexual men
  - 6.9% of cases among women
- Considered “safe sex” especially by younger people. Isn’t.
  - Condoms rarely used in oral sex
  - Remember that 30% of genital HSV is now HSV-1
  - 70% of newly acquired cases

Simultaneous 1º and 2º Syphilis

- Normal host: 33%
- HIV: 75%

Presence of *Treponema pallidum* in CSF in early syphilis

- Primary 40% (8/20)
- Secondary 23% (15/66)
- Early latent 20% (9/45)
- Overall 24.4% (95% CI~18-33%)


Significance of *T. pallidum* in CSF in early syphilis

- Did not increase the rate of serologically defined treatment failure with standard treatments
- Posttreatment detection of *T. pallidum* in CSF was not more common in patients with HIV infection than without HIV infection
- Don’t do LP in HIV positive patients with early syphilis and CD4>350


When should the CSF be examined?

- If neurological or ophthalmic signs or symptoms are present (duh)
- Active tertiary syphilis (e.g. aortitis, gumma)
- Treatment failure
  - Failure of nonreponemal titer to fall after 2 years
  - Subsequent 4X rise in nonreponemal titer without evidence of reinfection
- Syphilis of undetermined duration?? (MFR)
  - Some specialists: Advanced HIV (CD4 ≤ 350/ml) or RPR ≥ 1:32
  - Not associated with improved clinical outcomes

CDCP: MMWR 2010;59(RR-12): 26-36

CSF exam in asymptomatic HIV+ patients with syphilis

- 202 men, no neurological signs or symptoms, retrospective chart review
- Prevalence of asymptomatic neurosyphilis
  - Late, latent, unknown duration 8/39 (22%)
  - CD4 ≤ 350 and/or RPR titer ≥ 1:32 10/43 (23%)
  - Serological treatment failure 4/13 (21%)
    - Increased RPR titer
    - Failure of 4x drop
- Each of these is a good criterion for LP


Two basic types of serological tests for syphilis

- Nontreponemal (e.g. VDRL, RPR)
  - Use extract of beef heart as antigen
  - Cheap
  - Can be quantitated
  - Non specific - frequent false positives
  - Sometimes insensitive
- Treponemal (e.g. FTA-abs, MHA-Tp, TpPA, CAPTIA Syphilis-G)
  - Use parts of *T. pallidum* as antigen
  - Many techniques
  - More sensitive, more specific
  - More expensive
Uses of Tests for Syphilis

- Classical: Nontreponemal first, and if positive go on to treponemal
- Newer: Treponemal first, and if positive go on to nontreponemal for quantitation
- Followup on therapy:
  - Nontreponemal only (must use same test throughout)
  - RPR may yield higher titers than does VDRL
  - Q3 months to fourfold drop
  - Annually to stable titer

RPR titers following Rx

- CDCP Recommendations – HIV negative
  - Primary and secondary syphilis: 6 months and 12 months
  - Early latent syphilis: additional at 24 months
- Interpretation
  - ≥ 4X drop: cure
  - ≥ 4X rise: relapse or reinfection
  - ≤ 2X drop or rise: serofast

CDCP: MMWR 2010;58(RR-12):26-34

RPR titers following Rx (MFR)

- Consider initial followup at 3 months
  - Eliminate 75% of patients requiring additional acute follow-up
  - Reduce loss to follow-up
  - Reinforce safe-sex practices
  - Check for chlamydial/gonococcal reinfection
  - Evaluate for HPV
  - Still want to do long term serological follow-up to document lowest titer

Serologically defined cure

- All treatments: penicillin and azithromycin
- ≥ 4X drop in RPR titer

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
</tr>
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<tbody>
<tr>
<td>Primary (N=116)</td>
<td>85.5%</td>
<td>87.0%</td>
</tr>
<tr>
<td>Secondary (N=217)</td>
<td>82.5%</td>
<td>85.8%</td>
</tr>
<tr>
<td>Early latent (N=132)</td>
<td>54.5%</td>
<td>62.1%</td>
</tr>
</tbody>
</table>

- Little increase between 6 and 12 months
- Early latent less responsive (Followup at 24 months)

### Advantages of treponemal first
- More sensitive than nontreponemals (VDRL, RPR) in most stages of syphilis
  - Not entirely true in primary syphilis
- More specific than nontreponemals
  - But Bayes’s theorem will still hurt you in a very low prevalence population: low positive predictive value
- Can be automated, reducing technician time and increasing throughput


### Disadvantages of treponemal first
- Confusion regarding approach to discrepant trep+/nontrep- tests
- Lower positive predictive value than when it follows reactive RPR (Bayes again)
- Currently higher cost in low-prevalence populations
  - Use traditional approach in low-volume laboratories
- Stays positive after adequately treated infection


### Comparison of algorithms

<table>
<thead>
<tr>
<th></th>
<th>RPR-1st</th>
<th>ECDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.76</td>
<td>.994-.999</td>
</tr>
<tr>
<td>Specificity</td>
<td>.998-1.00</td>
<td>.999-1.00</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td></td>
<td>.999-1.00</td>
</tr>
</tbody>
</table>


### Common Problems with Syphilis Serology
- May not be positive at time of appearance of the chancre
- Prozone phenomenon in secondary syphilis
- Treponemal tests stay positive even after adequate treatment
- Nontreponemal tests may become negative in late syphilis
Diagnostic tests in 1° syphilis

- 5.4% of all cases at Baltimore STD Clinic were darkfield + but RPR –
- Sensitivity of nontreponemal tests in 1° syphilis
  - VDRL 60-75%
  - RPR 86%


False positive treponemal tests in Lyme Disease

- Maragoni: J of Clin Lab Analysis 2009; 23: 1–6
  - 1/10 10% (95% CI: 0.00-30.85)
- 2011 unpublished data on Syphilis Health Check™, a new, treponemal test
  - 1/25 4% (95% CI: 0.10-25.35)
- Very small numbers: This space reserved for future data (?)

The Prozone Phenomenon

- Not seen with treponemal tests
- Seen in ~2% of serologic tests
- Antibody excess in very high titers
  - No lattice formation
  - Especially in 2° syphilis
  - So a cause of trep+/nontrep-
- Diagnosed by automatically diluting out nonreactive RPRs
  - Beware of private labs

Interpretation of the two tests

- Treponemal reactive + nontreponemal reactive = past or present syphilis
  - Or: yaws, pinta, bejel
- Nontreponemal reactive + treponemal nonreactive = biological false positive
  - No need to work up if an isolated finding
- Treponemal reactive + nontreponemal nonreactive = ??????
Treponemal +/- Nontreponemal -
- Early primary syphilis
- Prozone phenomenon
- Late syphilis
  - Tabes
  - Paresis
- Adequately treated syphilis
- Lyme disease

Treponemal +/- Nontreponemal -
- Treat patients not lab tests
- Very careful history and physical examination
  - Especially Hx of prior syphilis
  - Hx of other STD
- Consult Reactor File (call Health Dept)
- Consider different treponemal test (CDC)
- Evaluate sexual partners

Reverse serology at UVA 2012
Courtesy: Walter Olivera

- Syphilis Bioplex IgG 6473
  - Reactive 235 (3.6%)
  - Equivocal 18 (0.3%)
- Reflex RPR 253
  - Reactive 85 (34%)
  - Nonreactive 168 (66%)
  - Previously reactive (i.e. treated) 28
- TPPA 140
  - Reactive 78 (56%)
  - Nonreactive 62 (44%)

Treponemal+/Nontreponemal-
- History of previous syphilis therapy:
  - No further treatment indicated
  - If high-risk behavior, may follow for increasing RPR titer
- No prior history of syphilis treatment
  - Perform additional treponemal test (TP-PA, FTA-ABS)
    - Preferably one based on a different antigen
  - If positive, treat for late-latent syphilis
  - If negative, consider yet another treponemal test
- Supporting data, see appendix

CDC:MMWR 2008;57:872-5
One of the things that penicillin still does is treat syphilis

Penicillin remains the treatment of choice for all stages of syphilis

**Benzathine Penicillin (Bicillin®)**
- Make sure to use Bicillin L-A, not Bicillin C-R
- *Clostridium difficile* infection has been reported after use of benzathine penicillin G
  - No surprise
  - Remember, you can’t “discontinue” benzathine PCN for about 3 weeks


---

**Treatment of early syphilis in penicillin allergy**
- Pregnancy: desensitize to penicillin
- Ceftriaxone 1 gm intramuscularly daily for 8-10 days
  - Unless allergy is IgE-mediated (i.e. anaphylaxis), in which case all β-lactams are contraindicated
- Doxycycline 100 mg orally, twice daily for 14 days
- Azithromycin 2 gm orally as a single dose

CDCP: MMWR 2010; 59:30

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**Treatment of Primary Syphilis with a Tetracycline**
- Retrospective review
- 445 cases of primary syphilis
  - 420: Benzathine penicillin
  - 25: Oral tetracycline for 14 days
    - Doxycycline 100 mg twice daily
    - Tetracycline 400 mg 4 times daily

Wong: Amer J Med 2008;121:903-8
Treatment of Primary Syphilis with a Tetracycline

- Serological cure
  - Tetracycline: 25/25 (100%)
  - Penicillin: 409/420 (97.4%)
- Estimated time to serological response
  - Penicillin: 72 days
    - observed mean 102 d
  - Tetracycline: 43 days
    - observed mean 79 days

GOOD NEWS: There is (yet) no evidence of tetracycline resistance in *T. pallidum*

CAUTIONS
- Compliance, compliance, compliance
- Very small numbers for tetracyclines
- May be bacteriostatic for *T. pallidum*: watch out in HIV/AIDS

Wong: Amer J Med 2008;121:903-8

Azithromycin 2gm for Early Syphilis

- N=517, US and Madagascar, HIV-negative
- 1°, 2°, and Early Latent syphilis
  - RPR and FTA-ABS reactive
  - 1° = chancre
  - 2° = rash
  - EL: within past year: negative RPR or contact with lesion syphilis
- 2 gm azithromycin po, 2.4.MU benzathine penicillin im
- Endpoint 4X drop in RPR titer


Azithromycin 2gm for Early Syphilis

<table>
<thead>
<tr>
<th>N</th>
<th>4-fold drop at 3 mo</th>
<th>4-fold drop at 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithro</td>
<td>238</td>
<td>74.4%</td>
</tr>
<tr>
<td>Pen</td>
<td>247</td>
<td>75.7%</td>
</tr>
<tr>
<td>Per protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithro</td>
<td>218</td>
<td>73.4%</td>
</tr>
<tr>
<td>Pen</td>
<td>232</td>
<td>74.9%</td>
</tr>
</tbody>
</table>

Factors favoring spread of macrolide resistant *T. pallidum*

- Introduction of resistant organism into high-risk sexual networks
- Use of azithromycin in high-risk groups:
  - Chlamydial infection
  - MAC prophylaxis
- Use of macrolides in the general infectious disease population


Jarisch-Herxheimer Reaction

- Clinical features
  - Acute onset hours after treatment of syphilis
  - Fever
  - Rash
  - Increased (return of) adenopathy
  - Myalgia
  - Flushing
  - Hypoentsion (occasionally serious)

Jarisch-Herxheimer Reaction

- Risk factors
  - Early syphilis: 82% vs 28 % (p<.001)
  - RPR ≥ 1:32: 82% vs 56% (p<.001)
  - No prior syphilis treatment: 32% vs 15% (p<.001)
  - Younger age (surrogate marker for above?)
    - JHR: 31.5 yrs
    - No JHR: 38.5 yrs
    - p<.001
  - No HAART: 68% vs 59% (p = .09)


Syphilis in HIV

- Serologic tests usually behave well
- No regimens have been shown more effective in preventing neurosyphilis in HIV-infected patients than the standard regimens (!)
- HIV-infected patients with late-latent syphilis or syphilis of undetermined duration should undergo CSF examination
Symptomatic Early Neurosyphilis Among HIV+ MSM

- 49 cases/30 months; 37 definite/10 probable
- Risk 1.7%,
- 47% had secondary syphilis
- 10% developed secondary within one week
- 24% early latent
- 18% “late latent” (some probably early)
- Therefore 53% had no other signs of syphilis

MMWR 2007 (June 29);56:625-8

Symptomatic Early Neurosyphilis Among HIV+ MSM

- Clinical features:
  - Visual disturbances 51%
  - Headache 32%
  - Gait disturbance 4%
  - Hearing loss 4%
  - Meningismus 2%
  - Altered mental status 2%

Therefore consider syphilis when you see
- Cranial nerve dysfunction
- Especially visual disturbances

MMWR 2007 (June 29);56:625-8