Sexually Transmitted Diseases: Hiding in Plain Sight?

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A 21 year old woman comes to clinic asking for STD tests. You’ll order:

- Depends on how many partners she’s had
- Depends on her symptoms
- Urine Gonorrhea/Chlamydia
- Cervix Gonorrhea/Chlamydia
- Throat Gonorrhea/Chlamydia
- Blood for syphilis
- Blood for HIV
- Urine for *Mycoplasma genitalium*
- Herpes antibody test
STD are increasing! 2018 in US:

1.7 million cases of chlamydia
580,000 gonorrhea
115,000 syphilis
1306 congenital syphilis: 185% increase since 2014

http://www.cdc.gov/std/stats/default.htm
Different Organisms, Similar Diseases

- **Chlamydia**
  - Urethritis
  - Cervicitis
  - PID
  - Epididymitis
  - Proctitis, prostatitis?
  - Conjunctivitis, trachoma
  - Reactive arthritis
  - Neonatal pneumonia, conjunctivitis

- **Gonorrhea**
  - Urethritis
  - Cervicitis
  - PID
  - Epididymitis
  - Proctitis
  - Conjunctivitis
  - Pharyngitis
  - Disseminated infection
  - Neonatal conjunctivitis

**Majority of all infections have no symptoms!**
Urethritis: Inflammation of the Urethra

Symptoms/signs:
- Urethral discharge
- Dysuria
- WBC (>5/highpower field)

May progress to epididymitis

Causes:
- Gonorrhea
- Chlamydia
- Mycoplasma genitalium
- Trichomonas
- Herpes
- Other??
Cervicitis: may have vaginal discharge, bleeding, or no symptoms

Pelvic Inflammatory Disease: abdominal pain, leads to scarring of fallopian tubes

Causes: chlamydia, gonorrhea, maybe other mixed flora, mycoplasmas, etc.
Complications of Chlamydia and Gonorrhea in Women

- Ectopic pregnancy
- Infertility
- Chronic pelvic pain
- Silent PID
- Acute PID

Untreated infection

Screening and treating for asymptomatic infection is cost-saving!

Elaine Thomas, MD
Yearly Chlamydia Screen for Any Woman Who:

Is sexually active and age $\leq 25$

Is sexually active, of any age, and:

- Has had an STD before OR
- Has more than one sexual partner OR
- Does not use condoms consistently and correctly

Guideline endorsed by CDC, AMA, American Acad. of USPS Task Force, ACOG, etc.

Proven to reduce PID  \((\text{NEJM 334:1362, 1996})\)

Less than half of eligible women get screened!
Nucleic-acid Amplification Tests for Gonorrhea and Chlamydia

• Very sensitive
• Urine, urethral, cervical, vaginal, anal, pharyngeal
  • Triple screen for MSM
• Can screen asymptomatic males
• Can use in non-clinical settings
• Can self-collect
• DOESN’T test for resistance
• Know what kind of test your lab offers

Extragenital sites in women: *Sex Transm Dis.* 42:233, 2015

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Chlamydia Treatment: CDC 2015 guidelines

Recommended regimens:
- Azithromycin 1 g PO x 1 (watch for vomiting)
- Doxycycline 100 mg PO BID x 7 d (watch for nonadherence)

Alternatives:
- Erythromycin base 500 mg PO QID x 7 d
- Erythromycin ethylsuccinate 800 mg PO QID x 7 d
- Ofloxacin 300 mg PO BID x 7 d
- Levofloxacin 500 mg PO QD x 7 d

• Good review of concerns about equivalence of doxy and azithro:
  Dombrowski et al., Sex Transm Dis 43: 603, 10/2016
Gonorrhea: evolution of resistance
Has acquired multiple plasmid and chromosomal resistance mutations

Now rare reports of gonorrhea resistant to all antibiotics usually used!
Adapted from Workowski et al., Ann.Int.Med 2008, 148(8):606

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Gonorrhea Treatment:  [www.cdc.gov/std/gonorrhea/](http://www.cdc.gov/std/gonorrhea/)

**Uncomplicated gonorrhea of cervix, urethra, or rectum**
Ceftriaxone 250 mg IM once *PLUS*
Azithromycin or doxycycline as for chlamydia
(EVEN if chlamydia test negative)

**Alternative regimens:**  ONLY IF ceftriaxone not available:
Cefixime 400 mg single oral dose  *PLUS*
Azithromycin or doxycycline as for chlamydia
*PLUS*  Test of cure in 1 week

**Serious cephalosporin allergy:**
Consult expert, and test of cure
**Gonorrhea and Chlamydia: Re-testing after treatment**

- Test of cure not needed unless pregnant or second-line tx
- Nucleic acid amplification tests positive up to 2 weeks after treatment (CID 62:1348, 2016)

- Re-infection rate
  - Chlamydia - women 7-25%; men 13%;
  - Gonorrhea - women: 12-24%; men 9%

- Retesting recommendation (CDC)
  - Women: retest 3 mo after treatment, or at next visit within 12 mo
  - Less evidence for men (suggest retest in 3 mo)
A young man who has had sex with multiple men comes in with urethral burning and a scant penile discharge. You treat him with azithromycin. His tests come back negative for GC and CT. He comes back a month later. His symptoms got a little better but then came back.
Mycoplasma genitalium: uncertain significance!

• Organism associated with urethritis, cervicitis, PID, preterm birth, infertility, HIV transmission
• But LESS strongly than CT and GC, so causative role uncertain
• New nucleic amplification test recently approved
• Screening NOT currently recommended
• Consider testing symptomatic cases, especially if failing treatment
• Poor response to doxycycline; increasing resistance to azithromycin
  • Moxifloxacin? - though some resistance reported

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Primary and Secondary Syphilis: Rates of Reported Cases by County, 2018

* Per 100,000.
† In 2018, 1,498 (47.7%) of 3,142 counties in the United States reported no cases of primary and secondary syphilis. See section A1.4 in the Appendix for more information on county-level rates.
Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2018

* Per 100,000.
† Log scale.
Why isn’t Syphilis gone?

• Easy to treat – no antibiotic resistance
• Targets people with less access to health care
• Can’t be seen on Gram stain or grown in the lab
• Long periods with no symptoms, yet causes serious disease
• Diagnosis depends on serology (blood antibody) tests with many pitfalls in interpretation
Syphilis Serology

- Traditionally: nontreponemal first, if positive confirm with treponemal
- Some labs now do a new treponemal Ab first

<table>
<thead>
<tr>
<th>Nontreponemal</th>
<th>Treponemal</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPR, VDRL</td>
<td>TPPA, MHA-TP, FTA, new Trep-Sure</td>
</tr>
<tr>
<td>Quantitative</td>
<td>Qualitative</td>
</tr>
<tr>
<td>Titers go down with treatment – Can be negative in early or late disease</td>
<td>Stays + for life, with or w/o treatment</td>
</tr>
<tr>
<td>False positives and negatives</td>
<td>More specific</td>
</tr>
</tbody>
</table>
Table 2. Sensitivity and Specificity of Treponemal Assays for Detection of Syphilis, by Stage and Overall

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity by Stage</th>
<th>Overall Sensitivity</th>
<th>Overall Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Primary n = 55)</td>
<td>(Secondary n = 98)</td>
<td>(Early Latent n = 41)</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>78.2(^a) (65.0–88.2)</td>
<td>92.8(^a) (85.7–97.0)</td>
<td>100 (90.7–100)</td>
</tr>
<tr>
<td>TPPA</td>
<td>94.5 (84.9–98.9)</td>
<td>100 (96.2–100)</td>
<td>100 (90.7–100)</td>
</tr>
<tr>
<td>Centaur CIA</td>
<td>94.5 (84.9–98.9)</td>
<td>100 (96.2–100)</td>
<td>100 (90.7–100)</td>
</tr>
<tr>
<td>Trep-Sure EIA</td>
<td>94.5 (84.9–98.9)</td>
<td>100 (96.2–100)</td>
<td>100 (90.7–100)</td>
</tr>
<tr>
<td>LIAISON CIA</td>
<td>96.4 (94.5–98.2)</td>
<td>100 (96.2–100)</td>
<td>97.6 (87.4–99.9)</td>
</tr>
<tr>
<td>Bioplex MBIA</td>
<td>96.4 (94.5–98.2)</td>
<td>100 (96.2–100)</td>
<td>95.1 (83.8–99.4)</td>
</tr>
<tr>
<td>INNO-LIA</td>
<td>96.4 (94.5–98.2)</td>
<td>100 (96.2–100)</td>
<td>100 (90.7–100)</td>
</tr>
</tbody>
</table>

Data are presented as % (95% confidence interval).

Abbreviations: CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption test; LIA, line immunoassay; MBIA, microbead immunoassay; TPA, *Treponema pallidum* particle agglutination assay.

\(^a\)FTA-ABS was less sensitive than other assays for primary syphilis (all \(P < .01\)) and secondary syphilis (\(P = .007\)). Combining all stages, FTA-ABS was less sensitive than TPPA (\(P = .038\)) or the immunoassays (all \(P < .001\)).

\(^b\)TPPA significantly less sensitive than Trep-Sure EIA for late latent syphilis (\(P = .009\)); all other comparisons were not statistically significant.

\(^c\)Trep-Sure EIA was significantly less specific than all other assays (all \(P < .001\)).
Syphilis: Primary Chancre

Images from: *STD Atlas, 1997*
Rash of Secondary Syphilis – can look like anything!!
Secondary Syphilis: Other clues

Condyloma lata

Mucous patches


Patchy alopecia
Determining syphilis stage is critical for management

Incubating syphilis
   Recent exposure, may be infected; blood test may not be positive yet
Primary: 3-6 weeks after infection - Chancre, localized lymphadenopathy
Secondary: 6-12 weeks after infection
   Rash, lymphadenopathy, fever, mucous patches, alopecia, headache, hepatitis, nephritis, etc.

Early Latent
   No signs and symptoms, < 1 year after infection
   Can still be infectious; secondary signs may recur
   TX: LA Bicillin x 1

Late Latent
   No signs and symptoms, > 1 year after infection
   Less infectious, symptoms probably will not recur

Latent unknown duration
   Positive serology, no signs/symptoms, unknown time of infection
   TX: LA Bicillin x 3

Tertiary Syphilis – years later: neurological, cardiovascular, gummatous lesions

Neurosyphilis
   Can happen at ANY stage
   Eye or ear disease - treat same as neurosyphilis
   TX: IV penicillin 14 days

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Syphilis in Pregnancy

• Screen ALL pregnant
• Transmission more common in 2nd & 3rd trimester
• Treatment effective if completed in time
• Outcome in untreated early syphilis
  • 25% intrauterine death
  • 25% perinatal death
  • 50% congenital syphilis
• How does congenital syphilis happen?:
  • No prenatal care
  • Incomplete, late, or interrupted care
  • Misinterpretation or miscommunication of tests
  • Woman infected after testing
  • Wrong, too-late or incomplete treatment
Many Bad Outcomes – Early and Late
Testing in Pregnancy

- All women must be tested at first prenatal visit
- Either treponemal or nontreponemal screen
- False positives do happen, need careful evaluation
- “High-risk” women or those in “high-risk area” should be tested again in 3rd trimester and at delivery
- No newborn should leave hospital without maternal tests known
Syphilis Management: CDC Guideline

• Careful history and exam, including neurologic, eye
• Treat according to disease stage
• Followup RPR at 3, 6, 12 months to look for 4-fold drop
• Penicillin allergy? Take a good history; many are not truly allergic
• Doxycycline alternative if PCN-allergic, except:
  • Pregnancy or neurosyphilis – ONLY pencillin; get expert advice!
  • Pregnancy: RPR monthly till delivery; coordinate with OB and Pediatrics
• Help from Health Department to ensure partners treated
Herpes Simplex

• Type 1 *usually* oral, Type 2 *usually* genital
• US adult HSV-2 Seroprevalence (NHANES): 17%
• Most who have it don’t know it
• Can be transmitted by asymptomatic shedding
• Can seriously infect neonates – skin, CNS, or disseminated (rare)
• Acyclovir, valacyclovir, famciclovir:
  • episodically for outbreaks or
  • daily for suppression
Trichomonas  (a CDC “neglected parasite”)

- Prevalence: ~3% in women 14-49 yo; older age range than gonorrhea and chlamydia
- Many asymptomatic
- Associated with:
  - postpartum endometritis, low birth weight, preterm labor, PROM
  - HIV transmission/acquisition
- Metronidazole resistance increasing though still uncommon
  - Higher dose metronidazole or tinidazole may cure
- No great options for true metronidazole allergy – consider desensitization
- Metronidazole-alcohol interaction is probably rare
- 500 mg BID x 7 days better than 2 gm x 1
- Topical metronidazole less effective
- Must treat the partner(s)!
- Diagnosis in men has been a barrier; Tricore Lab can do on urine

Human Papilloma Virus and Genital Warts

• Very common; mostly asymptomatic
• Some strains mostly warts, others cause dysplasia/cancer
• Infection, and warts, may spontaneously resolve
• Worse in immunocompromised
• Vaccine is very effective and safe!

Principles of STI Management

• Follow CDC treatment guidelines
  • www.cdc.gov/std/treatment/default.htm
• Test patient for other STI, including HIV
• Notify Public Health Department (reportable diseases)
• Evaluate and treat all recent partners
• Educate patient: treatment failure, prevention, rescreening
• Condoms reduce risk
• Discuss HIV PrEP if at risk

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What will you do differently as a result of this talk?

- Screen more young people routinely for GC/CT?
- Check what kind of GC/CT test your facility uses? Throat/rectal?
- Test for syphilis and HIV too?
- Check whether your lab uses treponemal or nontreponemal test?
- Ask patients more about their sexual history?
- Find out where people can get PrEP in your area?
- Re-test patients 3 months after a GC or CT diagnosis?
- Re-test pregnant women in 3rd trimester and at delivery?
- Education/outreach about STD to your community?
Resources and Reading

CDC STD 2015 Treatment Guideline: www.cdc.gov/std/treatment/default.htm

STD Prevention Training Centers - resources and online self-study, for example: http://californiaptc.com/online-learning/ and https://www.std.uw.edu/

CDC self-study: http://www.cdc.gov/std/training/std101/home.htm

USPS Task Force: https://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-recommendations-for-sti-screening

New Mexico Expedited Partner Therapy guideline: https://nmhealth.org/publication/view/help/1602/

Herpes review: Gupta et al., Lancet 370:2127, 2007


Lutz AR, LGBT Health. 2015;2:27. Screening for Asymptomatic Extragenital Gonorrhea and Chlamydia in Men Who Have Sex with Men: Significance, Recommendations, and Options for Overcoming Barriers to Testing.


JAMA, “Why are mothers still passing syphilis to their babies?” https://jamanetwork.com/journals/jama/article-abstract/2724373