

Sexually Transmitted Infections

Donna Felsenstein, M.D.

Director, STD/GID Unit Massachusetts General Hospital

Physician in Medicine, Massachusetts General Hospital

October, 2015

MMWR
Sexually Transmitted Diseases
Treatment Guidelines, 2015

<http://www.cdc.gov/std/tg2015/default.htm>

Sexually Transmitted Pathogens

Bacteria:	<i>N. gonorrhoeae</i> , <i>H. ducreyi</i> , <i>K. granulomatis</i>
Spirochetes:	<i>Treponema pallidum</i>
Chlamydia:	<i>C. trachomatis</i>
Mycoplasma:	<i>M. hominis</i> , <i>M. genitalium</i> , <i>U. urealyticum</i> , <i>U. parvum</i>
Viruses:	HSV, HPV, Molluscum, HIV, Hepatitis A, B, C, Adenovirus
Protozoa:	<i>T. vaginalis</i> , <i>E. histolytica</i> , <i>G. lamblia</i>
Fungi:	<i>C. albicans</i>

Incidence of STDs

20 Million new cases annually
\$16 Billion

Taking a Sexual History: Who Would YOU Ask?

- a) Heterosexual college man in a monogamous relationship with a woman for 3 years?
- b) 50 year old housewife with chronic fatigue syndrome?
- c) 55 year old married female executive with recurrent urinary tract infections?
- d) 65 year old business man with osteomyelitis?
- e) 25 year old man who has sex with men?
- f) all of the above

True or False

Most people with a sexually transmitted infection will have symptoms and seek medical care

The vast majority of
people with an STD
have **no** recognizable
symptoms

1 in 4 Teen Girls
Has a Sexually
Transmitted Disease

March 11, 2008

Screening of Adolescents

- High school population
- Self-collection of vaginal swabs
- 8%+ chlamydia, 2%+ GC, 10%+ trich, (PCR)
 - Overall 18%+
- 13% of those who never had a gyn exam tested +
32% of those positive never had a pelvic exam
- 87% did not think they had an STD
- 51% would not have sought care

STUDY:

Ongoing Sexually Transmitted Disease Acquisition and Risk-Taking Behavior Among US HIV-Infected Patients in Primary Care: Implications for Prevention Interventions

Mayer KH et al. STD 2012: Vol 39 (1)

Prospectively followed 557 HIV+ men and women
Tested at enrollment and 6 mos.

Baseline:

13% had at least 1 STD; all were asymptomatic

6 months:

7% developed at least 1 new STD

Majority of STDs were in MSM;

Rectal CT was most common

Screening Men who have Sex with Men (MSM)

- Assess the sex of sexual contacts for ***all*** male patients
- **Annual Screening**
 - HIV serology
 - Syphilis serology
 - Urethral/Rectal testing for GC, Chlamydia
 - Pharyngeal GC
 - ? Anal pap
 - ? HSV 2

Screening Men who have Sex with Men (MSM)

- **Screening q 3-6 months**
 - MSM with multiple or anonymous contacts
 - Use of illicit drugs; Methamphetamines
 - Sexual partner/contact participates in risky behavior
- **Add'l :**
 - HbsAg
 - Hepatitis C
 - Hepatitis A, B vaccines

Screening Women who have Sex with Women (WSW)

- Risk varies by sexual practice
- Transmission of Human Papillomavirus (HPV) has been detected by PCR in 13-30% of WSW
- Transmission of syphilis by oral sex
- Transmission of HSV 1 > HSV 2
- Rate of transmission of C. trachomatis is unknown
- 53-99% of WSW have had sex with men

Screening for Women

- Up to age 25
 - Routine Chlamydia and GC screening
 - HIV/other STDs based on risk
- >25 yrs –
 - HIV/other STDs based on risk
- Pregnant
 - Chlamydia
 - GC (≤ 25 or at risk)
 - HIV
 - Syphilis
 - HepBsAg
 - HepC (if at risk)

Taking a Sexual History

1. Do you have sex with men, women, or both?
2. How many different people do you have sex with?
3. How many different people have you had sex with in the past 6 mos? A year? Lifetime?
4. Did you put your mouth on someone's penis, rectum, vagina?
5. Does someone put his penis in your vagina? Mouth? Rectum?

Taking a Sexual History

6. Do you birth control? What kind? Do you use it all the time?
7. Do you use condoms? With every person? All the time?
8. Do you use condoms at the start?
9. Have you ever had a sexually transmitted infection?

Approach to the Patient

- Physical Exam
- Laboratory Tests:
 - Cervical gram stain
 - Wet prep of vaginal secretions
 - Urethral gram stain
 - Specimens for gonorrhea
 - Specimens for chlamydia
 - Syphilis serology
 - HIV testing
- Education/counseling

Prevalence and Incidence of Pharyngeal GC in MSM

- Prospective study in MSM 2001-2003
- Screened every 6 months
- Prevalence of GC **5.5%**
- Incidence **11.2 per 100** person-yrs
- Pharyngeal GC was **asymptomatic in 92%**

Morris SR et al. Clin Inf Dis; 2006

Rectal Gonorrhoea

- Occurs in **30-50% of women with GC** and **40% of MSM**
- **Majority are *asymptomatic***; symptoms include: constipation, pain, tenesmus, anorectal bleeding, discharge
- Gram stain: positive in 60-80%
- Differential diagnosis:
 - Chlamydia(D-K), LGV, HSV1&2, Syphilis, Shigella, Campylobacter, E. Histolytica, giardia, CMV, Cancer

Disseminated Gonorrhea

- Occurs in **1-3%** of patients
- Incubation period: **7-30 days**
- Sx: fever, anorexia, malaise, skin lesions, tenosynovitis, migratory arthralgias, arthritis, hepatitis, myopericarditis
- Dx: blood cultures (25%)
- Culture mucosal sites: pharynx, rectum, urethral, cervical, synovial fluid

URINE TESTING IS NOT
ENOUGH

Gonorrhea - Dx

- **Culture techniques**
- **DNA probe**
- **Amplification techniques**
 - *Not FDA cleared:*
 - Rectum, pharyngeal, conjunctival;
 - Some labs have done validation testing enabling use for clinical care

THE EMERGING THREAT OF UNTREATABLE GONOCOCCAL INFECTION

Bolan GA, Sparling PF, Wasserheit JN
NEJM Feb, 2012

Treating Uncomplicated Urethral & Cervical GC

Increased MIC to cephalosporins

CEFTRIAXONE 250 mg IM

(99.2% urogenital/rectal; 98.5% pharyngeal)

PLUS

AZITHROMYCIN 1gm or DOXYCYCLINE (100 mg bid X 7 days)
(regardless of +/- for chlamydia)

Cefixime – 400 mg; (97.5%-urogenital; 92% pharyngeal)

Cefpodoxime 400 mg (pharynx: only 70%)

*Cefuroxime – not adequate (95% urogenital/rectal;
57% pharyngeal)*

ALL patients should be retested within 3 mos; or when they
return next within 12 mos

Treatment of GC Infections

- Gentamicin 240 mg IM/ azithromycin 2gm
100% genital GC infections
- Oral gemifloxacin 320mg/ azithromycin 2gm
99.5% genital GC infections

Both combinations cured 100% of infections of the **throat and rectum.**

Adverse effects: mostly gastrointestinal issues.

Case 1 - Bill Williams

- 24 year old man who has sex only with women c/o dysuria X 1 week
- He has had 2 female contacts within the past 4 months, the most recent one was 3 weeks ago. He thinks he used a condom, but can't remember as he had been drinking at a party.
- Denies discharge, frequency, urgency, hesitancy, fever

Case 1 – Bill Williams

- What tests do you do?
- How do you treat him?

NGU

- *C. trachomatis* 15-40%
- *M. genitalium* 15-25%
- *Ureaplasma urealyticum*,
Ureaplasma parvum
- *T. vaginalis*
- HSV
- Adenovirus
- ?Other mycoplasmas
- Other pathogens?

Chlamydia Trachomatis

- Most frequently reported infectious disease in the US
- Est. 3 million cases annually
- 1 out of 10 adolescent girls tested are infected
- Teenage girls have the highest rate of infection
- **15-19** year old girls represent **46%** of infections;
20-24 year olds: 33% of infections

Chlamydia: Infections in Men

- Urethritis
- Epididymitis
- Prostatitis
- Proctitis

Screening Recommendations for *C. trachomatis*: *Sexually Active Women*

- Vaginal (self-obtained)/Cervical specimens preferred over 1st void urines
- Screening asymptomatic women is cost-effective
- <20 yrs old: screen at any pelvic examinations ***and*** at least once/yr
- 20-24 yrs old: screen at least once/yr
- >25 yrs old: screen at least once/yr if at risk

Risk factors

- Inconsistent use of barrier method
- New or more than 1 sexual contact in the last 3 months
- New contact since last test
- Infected with another STD

Cervicitis

- > 10 WBC in vaginal fluid in the absence of trichomoniasis ? association with Chlamydia/GC
- Rule out upper tract infection: endometritis/PID
- Test for *C. trachomatis* and *N. gonorrhoeae* (NAAT) & Treat
- Assess for BV and *T. vaginalis*
- ?Utility of HSV testing

DX of Chlamydial Infections

- Serology
- Culture
- Rapid Assays: FA, ELISA, DNA probe,
NAAT
- Cytology

NAAT - Oropharyngeal and Rectal Gonorrhea and Chlamydia

- 1,110 MSM San Francisco STD Clinic
- **Pharyngeal: Chlamydia - 0.8%; GC - 8.3%**
- **Rectal: Chlamydia - 6.1%; GC - 8.2%**
- NAATs identified 63-100% of extragenital chlamydial and GC infections
- Culture identified 27- 44% of extragenital chlamydial and GC infections

Schacter J et al -2008

- *NAATs not FDA approved; but may be validated by lab for use*

Treatment of Chlamydia in Adults With Uncomplicated Urethral, Cervical or Rectal Infections

- AZITHROMYCIN 1 gram once
Or
- DOXYCYLINE 100 MG BID x 7 day
Or
- TETRACYCLINE 500 MG QID x 7 days
Or
- OFLOXACIN 300 MG BID x 7 days
Or
- LEVOFLOXACIN 500 MG DAILY x 7 day
Or
- ERYTHROMYCIN BASE 500 MG QID x 7 days

NGU – Treatment of Persistent Symptoms

- Metronidazole 2 g po
 - or
 - Tinidazole 2 g po
 - PLUS
 - Azithromycin 1 g po
-
- Moxifloxacin 400 mg po X 7 days
 - (M. genitalium)

Follow-up Chlamydia Testing

- NAAT < 3 weeks may be falsely positive (dead organisms)
- *Test of cure* not recommended except in pregnant women
 - Retest all pregnant woman 3-4 weeks after completing Rx
 - Retest in 3rd trimester as well
- Majority of post treatment infections are from **reinfection**
- Retest all men and women 3 months after treatment
If not possible, then retest all men and women when they are seen within the next 3-12 months

CASE – Charles W.

- A 24 year old MSM presents with 2 week history of mucopurulent discharge from the rectum. He has had 2 contacts in the past 2 months, 1 of which is his partner. He uses condoms with his partner.
- His exam is noted for a 2 cm tender lymph node in the left groin, and some mucous/blood around the anus.

- What is your differential diagnosis?
- What tests would you send?
- Would you give him any medication?

Lymphogranuloma Venereum (LGV) Proctitis

- Increasing # of cases in MSM
- *C. trachomatis* L1-L3
- Sxs: Rectal discharge (mucoid/hemorrhagic), anal pain, Constipation, Fever, Tenesmus, Chronic fistula formation/strictures
- Diff'l: *N. gonorrhoeae*, *C. trachomatis* (D-K), Syphilis, HSV 1 & 2, CMV, *Campylobacter*, *Shigella*, *E. histolytica*, Cancer
- Rx for LGV: Doxycycline 100 mg bid X 3 weeks

Update on Lymphogranuloma Venereum (LGV)

Diagnosis

- 1) Clinical findings
- 2) Culture or **NAAT** testing
 - NAAT: *not* specific for LGV
 - not* FDA approved for ulcer/rectal specimens
 - CLIA validation
- 3) **Serologic testing**: not specific
 - CF : $\geq 1:64$ supports the diagnosis
 - MIF: $> 1:128$

Causes of Genital Ulcers

- Syphilis (*T. pallidum*)
- Herpes Simplex Virus 1 & 2
- Chancroid (*H. ducreyi*)
- LGV (*C. trachomatis* L1-L3)
- Granuloma inguinale (*Klebsiella granulomatis*)
- HIV
- Noninfectious causes: trauma, fixed drug reactions, Behcet's

Trends in Syphilis in the US: 2001-2007

- Syphilis rate increased for the 7th year in a row
- P&S syphilis: 2.1 to 3.7/100,000 pop
 - 76% increase
- 64% of cases in MSM
- In woman: 0.8 to 1.1/100,000
- Congenital syphilis: 8.2 to 8.5/100,000 live births

Trends of Syphilis in China

- Virtually eliminated 1960 -1980
 - 0.2 cases/100,000 in 1993
5.7 cases/100,000 in 2005
 - Increase in rate of congenital syphilis;
Average yearly rise of 71.9%
 - 0.01 cases per 100,000 livebirths in 1991
 - 19.68 cases per 100,000 livebirths in 2005
- “The results suggest that a range of unique biological and social forces are driving the spread of syphilis in China.”

Syphilis-Epidemiology

- 55,000 new cases/year
- 30% risk after exposure by sexual contact
- Transmission: sexual contact, transfusion, ?Needles, kissing, transplacental
- Patients are infectious for up to 4 years

Primary Syphilis

- Incubation period: 3-90 days
- The chancre: clean based, painless
 - Indurated ulcer begins as a papule
 - May be extragenital
 - May be multiple
 - Unnoticed 15-30%
- Heals spontaneously 1-8 weeks
- Regional lymphadenopathy often present
- Diff'l dx: HSV, chancroid, LGV, fixed drug eruption, granuloma inguinale, Cancer
- Diagnosis: darkfield microscopy, serology

Secondary Syphilis

- Occurs **2-8 weeks** after the chancre;
 - chancre may still be present
- Systemic Sx are often present (fever, malaise, headache)
- Physical exam: generalized lymphadenopathy, mucous patches, hepatosplenomegaly, condylomata lata, alopecia, skin rash involves palms and soles, varies greatly

Syphilis-Stages

- PRIMARY
- SECONDARY
- LATENT
- TERTIARY:
 - CARDIOVASCULAR
 - GUMMA
 - NEUROLOGICAL

Serology

- **NONTREPONEMAL TESTS**

- VDRL
- RPR
- ART

- **TREPONEMAL TESTS**

- FTA-ABS
- MHA-TP
- TPPA
- TPI
- HATTS

ELISA Assays

- Automated
- May be more sensitive than the VDRL, RPR, MHA-TP in early syphilis
- May be less sensitive for latent syphilis
- More expensive than the hemagglutination tests, VDRL, RPR

Syphilis Serology

- Patient JS: New patient exam
- Syphilis serology:
 - Treponemal EIA: positive
 - RPR: negative

What to do?

What does this mean?

Latent Syphilis >1 Yr Duration

- Rule out neurosyphilis –
 - Exam
 - ?LP
- RX: Benzathine Penicillin G 2.4 million units IM weekly x 3 wks

Penicillin allergic patients

- Rule out neurosyphilis by exam and LP
- Tetracycline 500 mg qid x 30 days
- Doxycycline 100 mg bid X 30 days

Diagnosis of Neurosyphilis

- Clinical presentation
- Positive CSF VDRL
- Elevated CSF protein
- Elevated CSF cell count ($>4-5$ WBC/mm³)
 - ? Higher specificity in HIV + patient if WBC >20 /mm³

- Positive CSF FTA-ABS is not specific for neurosyphilis
- Negative CSF FTA-Abs makes neurosyphilis unlikely

Rx of Neurosyphilis

Aqueous crystalline PCN G

4 million u IV q 4 hr x 10-14 days followed by
Benzathine PCN IM weekly X 3 weeks

Or

Aqueous procaine PCN G

2.4 million u IM daily + probenecid x 10-14 days
followed by Benzathine PCN IM weekly X 3 wks

Repeat LP after Rx and q 6 months x 2 yrs

- All contacts exposed to **early** syphilis within the preceding year should be **TREATED**
- Contacts of patients with syphilis of **unknown duration with titers $\geq 1:32$** should be **TREATED**
- Contacts of patients with late syphilis should be evaluated

Rx of the HIV+ Patient with Syphilis

- **Early Infection:**
Benzathine PCN 2.4×10^6 U IM weekly
F/U 3,6, 9, 12, 24 mos post rx.
- **Late latent Infection:**
Benzathine PCN 2.4×10^6 U IM weekly x 3 wks
- **LP if any neurologic sx's present**
- **?LP** not routinely recommended unless
CD4 count ≤ 350 ; or RPR ≥ 32

Genital Ulcers

- Syphilis (*Treponema pallidum*)
- Herpes simplex (*HSV-2, HSV-1*)
- Chancroid (*H. ducreyii*)
- LGV (*C. trachomatis L1-L3*)
- Donavanosis (*K. granulomatis*)
- EBV, HIV
- Behcet's
- Fixed drug reactions

Chancroid

- Organism:** *Hemophilus ducreyi*
- Epidemiology:** Underdeveloped countries
<1000 cases/yr in US
Incubation: 3-10 days
- Signs/Sx:** Painful, nonindurated ulcer with
ragged edges, regional adenopathy
- Diagnosis:** Isolation in selective media
Gram stain—"tracking"
Azithromycin 1 g once
- Treatment :** Ceftriaxone 250 mg IM once
Ciprofloxacin 500 mg BID X 3 days
Erythromycin 500 mg PO QID x 7 days

Work-up of Genital Ulcers

- All patients should have an RPR/syphilis serology at the first visit and repeated in 1 and 3 mos (if negative initially)
- Consider **EMPIRIC Treatment** – syphilis
- Additional tests
 - Darkfield
 - Tzanck prep
 - HSV culture, HSV DFA, PCR
 - Gram stain of edge of lesion
 - Culture of *H. ducreyi*
 - Serology for LGV

- A 29 year old man present to your office with 3 sores on his penis. He has sex with both men and women. He has “insertive intercourse”. He uses condoms with some people, but not all.

What else do you want to know about his history?

What would you do now?

What tests would you order?

Would you give him any medication?

Human Papillomavirus

- **14 million** new infections annually in the US
- Cervical cancer is the **11th** most common cancer in women in the US
- **12,170** new cases of cervical ca and **>4200** deaths in women in the US in 2012
 - » Satterwhite STD 2013; ACS 222.cancer.org
- Second most common cancer and leading cause of cancer-related death in developing countries (screening programs not available)

Human Papillomavirus (HPV)

- Majority of mucosal HPV infection is asymptomatic and subclinical
- > 50% of sexually active women have been infected by one or more genital HPV genotypes

Human Papillomavirus

- Risk for cervical ca
- Over 75% of cervical ca contain HPV DNA
50% is HPV 16
- Low risk – 6, 11, 42, 43 44
- Intermed risk – 35, 45, 51, 52, 58, 59, 63,
66, 68
- High risk – 16, 18, 31, 33

HPV

- Median duration of infection in young women is **8 mos**
- **30%** persistence after 1 yr
9% after 2 yrs
- **Persistence of HRHPV** is highly associated with progression to precancerous lesions

HPV

- 83-95% of cases of anal cancer
- 20-50% of vulvar cancer
- 60-65% of vaginal cancer
- 30-42% of penile cancer
- Oral cancers

Parkin DM;Vaccine 2006

ORAL HPV

- NHANES 2009-2010
 - Men and women 14-69 examined at mobile sites; oral rinse
 - **Prevalence of oral HPV 6.9%**
 - **Men 10.1% vs. Women 3.6%**
 - No sexual contact 0.9% vs. sexual contact 7.5%;
 - Prevalence increased with # sexual contacts
(20% > 20 lifetime partners)
 - **Infection with HPV-16 detected in:
1% men and women = 2.13 million**

Oral HPV: A potential time bomb for Cancer development, Especially in Men

Deresinski, S. Infectious Disease Alert; Vol 31, March 2012

- HPV detected in 25% of head and neck squamous cell cancers and 90% associated with HPV 16.

Gillison ML. J Natl Cancer Inst 2000;92(9):709-720.

- **Incidence of HPV-assoc oral ca increased 225% from 1988-2004**
- Could incidence of oral cancers due to HPV exceed incidence of cervical ca due to HPV
- ?role of HPV vaccine

Screening – Anal paps

- ?Formal recommendations
- MSM
- Women with cervical ca
- Highgrade vulvar disease or ca
- All HIV+ men and women
- Patients with perianal HPV
- Transplant pts

HPV DNA Test

- Detects HPV “high-risk” types
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
- Adjunct to cervical cytology screening in women aged 30 yrs or more
- Management of women \geq 21yrs with equivocal cytology results (*atypical squamous cells of undetermined significance (ASC-US)*)

{Qiagen (13 high risk types),

Hologic Cerista, Roche Cobas HPV,

GenProbe Aptima HPV(14 high risk types),}

Human Papillomavirus Vaccine

- **9-Valent vaccine**

6,11,16,18,31,33,45,52,58

HPV 16 and 18 (70% of cervical, anal and genital cancers)

HPV 6 and 11 (90% of genital warts)

- **Quadrivalent HPV Vaccine** (GARDISIL™, Merck)

6,11,16,18,

- **Bivalent Human Papillomavirus Vaccine**

(CERVARIX, GSK)

16 and 18

- **Woman and Men age 9-26 years of age**

Human Papillomavirus Vaccine

- HPV infection is acquired soon after sexual activity begins
- Cumulative incidence of 40% w/in 16 mos after sexual activity
- **Goal is to immunize prior to initiation of sexual activity**
- Higher immune response in younger people – (10-14 yr old > response than 15-25 yr old; GSK vaccine)

HPV Can Be Transmitted Non-sexually

- Common disinfectants (alcohol, glutaraldehyde) not effective
- Bleach/Autoclaving

J Meyers; J Antimicrob Chemo; 2014

Trichomonas vaginalis - Dx

- Wet prep
- OSOM Trichomonas Rapid test (Genzyme)
- Affirm VP III (Becton Dickinson)
- Culture
- Amplification tests (men & women):
 - Amplicor (Roche), Aptima Combo 2 (Gen-Probe)

Trichomonas - Rx

- Metronidazole 2 g po or
- Tinidazole 2 g po

- Alternative
 - Metronidazole 500 mg po bid X 7 days

- Pregnancy
 - Metronidazole 2 g po

STDs Enhance HIV Transmission

- HIV DNA increased in men with GC urethritis
- 8 fold increase in HIV RNA in men with urethritis
- HIV DNA increased in cervical samples in women with GC, chlamydia, cervical-vag ulcers or cervical mucopus
- Decrease in HIV DNA after RX

Prevention of STDs/HIV

- CONDOMS – MALE/FEMALE
- AVOID NATURAL CONDOMS
- NON-LATEX CONDOMS FOR LATEX ALLERGIC PATIENTS
- MICROBICIDES – NOT EFFECTIVE
- CIRCUMCISION - EFFECTIVE

Circumcision prevents STDs/HIV

- 5534 HIV negative men enrolled in Rakai, Uganda

Results:

- HSV 7.8% (circumcized) vs 10.3%
- HPV 18% (circumcized) vs. 27.9%
- No significant difference in the acquisition of syphilis

[N Engl J Med. 2009 March 26; 360\(13\): 1298–1309.](#)

HIV Rx -- Prevention

- Pre-Exposure prophylaxis (PrEP)
- Antiretroviral rx for HIV infected persons to reduce transmission to partners
- Post-Exposure Prophylaxis

General Principles

- Patients with 1 STD often have another STD and should be screened appropriately
- All patients should have serology performed for Syphilis
- Contacts of patients with a STD should be evaluated and rx'd when indicated

- Screening for STDs should be performed on asymptomatic persons who are at risk for having an STD
- Identification of an STD in a patient can indicate increased risk behavior and risk for HIV
- STDs increase the risk for HIV transmission and/or acquisition

- RX of STDs may reduce the risk for HIV transmission
- ALL patients should be counseled on HIV infection and “safer” sex practices

How Can Practitioners Make a Difference?

- Education
- Prevention
- Screening
- Screening
- Screening
- Contact tracing and treatment
- Vaccine development