Extra-genital STIs: An update

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Disclosure:

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Off-Label Disclosure

• This presentation will include discussion of the following non-FDA-approved or investigational uses of products/devices:

• Oral and rectal testing for *N. gonorrhoeae* and *C. trachomatis* with:
  • Hologic Gen-Probe APTIMA Combo 2®
  • BDProbeTec™ ET
  • Roche COBAS® PCR
Objectives

• Review the importance of an accurate and updated sexual history

• Discuss methods of testing for extragenital STIs

• Review epidemiology of extragenital STIs and pathogens associated with various anatomic sites

• Discuss epidemiology of non-cervical HPV
Important Behaviors to Address

• Have they engaged in any type of sexual activity?

• Number, gender, type and HIV status of sexual partners

• Types of sexual activity (oral, vaginal, anal)

• Use of barrier methods (condoms, dental dams)

• Barriers to safer sexual practices

CDC. Incorporating HIV prevention into the medical care of persons living with HIV: recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 2003; 52(RR-12)
How common are extra-genital sexual behaviors?

• Males:
  – Active oral
    • Lifetime 77%
    • Last sex 27%
  – Passive oral
    • Lifetime 79%
    • Last sex 28%

• Females
  – Active oral
    • Lifetime 68%
    • Last sex 19%
  – Passive oral
    • Lifetime 73%
    • Last sex 28%

Oral sex amongst UK Youth
Stone et al. *Perspectives on sexual and reproductive health* 2006;38:6-12

- Jan 2003 - May 2005
- Survey of 1,373 young people (58% were 16) attending schools in the UK
- 56% female/44% male/95% heterosexual

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal sex</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>Received oral sex (non-virgins)</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>Received oral sex (virgins)</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Condom never used for fellatio</td>
<td>83%</td>
<td>77%</td>
</tr>
<tr>
<td>Sexual Activity</td>
<td>% Unprotected Partner</td>
<td>% Unprotected Partners HIV Negative or Unknown</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Oral Sex</td>
<td>86.0</td>
<td>63.9</td>
</tr>
<tr>
<td>Vaginal Sex</td>
<td>25.9</td>
<td>60.0</td>
</tr>
<tr>
<td>Receptive Rectal Sex</td>
<td>38.8</td>
<td>48.4</td>
</tr>
<tr>
<td>Insertive Rectal Sex</td>
<td>35.1</td>
<td>26.5</td>
</tr>
</tbody>
</table>

Case

- 49 yo HIV+ male (CD4 410, HIV VL <48) presents for routine HIV f/u visit
- Reports 4 days of urethral burning.
- 3 male partners in previous 2 months.
  - HIV+ and HIV- partners; +100% disclosure
  - Receptive and insertive anal and oral sex
  - Receptive and insertive fisting
  - No condoms or gloves
Case continued...

- **Treatment:**
  - Ceftriaxone 250mg IM x 1
  - Azithromycin 1gm po x 1

- RPR – nonreactive
- GC (pharynx) – positive
- GC (urine) – negative; CT (urine) – positive
- GC (rectum) – positive; CT (rectum) – negative
- Hepatitis C Ab reactive; HCV VL <undetectable
He would have been covered adequately anyway, right?

But what about the next scenario?
Case

- Gram stain: >2PMN/hpf; no GNID

- Treatment:
  - Azithromycin 1gm po x 1

Remainder of exam normal
Labs

- CD4 670 (29%); VL 2480
- UA – 1.033/mod LE/small bld/4-8 RBC/TNTC WBC; culture negative
- Urine CT positive
- Oral GC positive
- Rectal GC positive, CT negative
- RPR 1:32

Patient returned for treatment of gonorrhea...
And the asymptomatic patient ...
Case

- 25 yo HIV+ male (CD4 890, HIV VL not detected) presents for routine HIV f/u visit
- No complaints, routine labs
- On Genvoya, adherent
- 2 male partners in previous 12 months
  - No history of sexual contact since his diagnosis (6 months ago)
  - 1 HIV- partner, 1 HIV unknown
  - Insertive and receptive anal sex
  - No condoms
Case

- Rectal GC negative
- Rectal CT positive
- Urine GC/CT negative

- Returned to clinic for treatment with 1,000 mg azithromycin
- RTC in three months and testing not done; 12 month repeat testing negative urine/rectal GC/CT.
MSM

• At least annually:
  – HIV
  – Syphilis
  – Urethral NAAT for gonorrhea and chlamydia
  – Rectal NAAT for gonorrhea and chlamydia (if exposed)
  – Oral NAAT for gonorrhea (if exposed)
  – HbsAg (once then as needed)
  – Hepatitis C Ab (if HIV+)
  – HSV serologies (consider)

• More frequent testing (q3-6mo) if high risk or STD identified on testing

• Vaccinate for Hepatitis A and B and HPV!!

2015 CDC STD Treatment Guidelines
### Performance of NAATs for Diagnosis of Pharyngeal and Rectal Gonorrhea

<table>
<thead>
<tr>
<th>Test</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>phGC</td>
<td>rGC</td>
</tr>
<tr>
<td>Aptima (TMA)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ProbeTec (SDA)</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>Amplicor (PCR)</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>Culture</td>
<td>65%</td>
<td>72%</td>
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The Catch...

- NAATs are not FDA-cleared for rectal or pharyngeal specimens
- BUT verification testing can be done by labs to meet CLIA requirements
- Association of Public Health Laboratories has sample protocols ([www.aphl.org](http://www.aphl.org))
- Two commercial labs (Quest & LabCorp) currently provide GC/CT NAAT for rectal/pharyngeal specimens
Proportion of CT and GC infections MISSED among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009

- **Chlamydia**
  - Identified: 23%
  - MISSED: 77%

- **Gonorrhea**
  - Identified: 5%
  - MISSED: 95%

Marcus et al, STD Oct 2011; 38: 922-4
Proportion with concurrent negative urethral test

- Positive pharyngeal GC
- Positive rectal GC
- Positive pharyngeal CT
- Positive rectal CT

Proportion with concurrent negative urethral test

Patton ME, et al. CID 2014;58(11)1564-70
• Jin et al - after controlling for number of episodes of insertive and receptive nonseroconcordant unprotected anal sex, there was an independent association between HIV seroconversion and anal gonorrhea (adjHR = 7.12, 95% confidence interval [CI], 2.05-24.79).

• Pathela et al - 1 in 15 HIV-negative MSM with a documented gonococcal and/or chlamydial rectal infection were diagnosed with HIV within a year. Annual HIV incidence significantly higher among MSM with rectal infections (6.67%; 95% CI, 4.61%–9.35%) than among MSM without rectal infections (2.53%; 95% CI, 1.31%–4.42%).

Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada

Cephalosporin-Resistant Gonorrhea in North America
2015 STD Treatment Guidelines: Gonorrhea

• Recommended
  – Ceftriaxone 250 mg IM

  Plus (even if chlamydia test negative)

  – Azithromycin 1gm po x 1

** Doxycycline 100mg po BID x 7d removed from preferred
Gonorrhea Treatment Alternatives
Anogenital Infections

**ALTERNATIVE CEPHALOSPORINS:**
- Cefixime 400 mg orally once

**PLUS**
- Dual treatment with azithromycin 1 g orally once, regardless of CT

**IN CASE OF SEVERE ALLERGY:**
- Gentamicin 240 mg IM or 5mg/kg IM + azithromycin 2g PO
  - OR
- Gemifloxacin 320 mg orally + azithromycin 2g PO
Case

- NH is a 32 yo F with HIV diagnosed in 2004
  - Stable CD4 ct = 400; VL <50
- During routine follow-up visit, complains of a rash
- Has felt tired lately but otherwise denies specific complaints
Further history reveals that the patient has been sexually active with 5 male partners in the last month.  
She does not know that HIV status of her partners  
She practices receptive anal sex and oral sex but denies vaginal sex  
Condoms for anal sex only
What is the most appropriate next step?

1. Review medication list
2. Advise to stop using current laundry detergent and follow-up in 1 month
3. Perform an RPR/VDRL, oral testing for *N. gonorrhoeae* and anal testing for *N. gonorrhoeae* and *C. trachomatis*
4. 1 and 3**
Based on the patient’s history, where was the likely site of inoculation?

1. Rectum
2. Mouth
3. Vagina
4. Big toe
5. None of the above
Syphilis

- Bacterial STD:
  - Infectious agent: *T. pallidum*

- Stages:
  - Primary
  - Secondary
  - Latent stages
Syphilitic nodules on the tongue
Joan Dalmau, MD et al
J Am Acad Derm
“The only thing you can’t get from oral sex is pregnant.”

... but what are the risks of various STDs?
Oral Sex Pathogen Risk

- Viral (HSV, HPV)
- Bacterial (Gonorrhea, Syphilis)

- Less risky: Chlamydia (pharyngeal chlamydia, urethral risk less well known), HIV
Anal Sex Pathogen Risk

- **Viral (HSV, HPV)**
  - Very prevalent but we don’t screen asymptomatic individuals
- **Bacterial (Gonorrhea, Syphilis, Chlamydia)**
- **HIV efficiently transmitted**
  - Hep C (HIV positive MSM)
- **Less risky: Trichomonas (< 0.6%; needs vaginal milieu)**
Who gets Extragenital STIs?

- **MSM**
  - Rectal gonorrhea: 5.9%
  - Pharyngeal gonorrhea: 4.6%
  - Rectal chlamydia: 8.9%

- **Women**
  - Rectal gonorrhea: 1.9%
  - Pharyngeal gonorrhea: 2.1%
  - Rectal chlamydia: 8.7%

- **MSW**
  - Rectal gonorrhea: 3.5%
  - Pharyngeal gonorrhea: 2.2%
  - Rectal chlamydia: 7.7%
Oral HPV
"No. Because without wanting to get too specific, this particular cancer is caused by HPV, which actually comes about from cunnilingus, ... But yeah, it's a sexually transmitted disease that causes cancer."

- Michael Douglas
Oral Cancer and HPV

• Associated with better prognosis

• HPV tumor status is the strongest individual predictor of survival
  – 30% absolute increase

Oral HPV

• Increasingly recognized as a cause of a subset of SCC of the oral cavity
  – Oral Cavity 23%
  – Oropharynx 35%
  – Tonsillar 90%

• Heavily influenced by birth cohort effect
  – Lower age
  – Gender

Oral Cancer and HPV

Sites most likely to be HPV-related include subsites of the Waldeyer ring, including the soft palate, palatine and lingual tonsils.
Head and Neck Cancer - Epidemiology

• Estimated 49,260 new cases of HNC diagnosed in US in 2010
• Incidence higher in males vs females
• Median age 7th decade though lower for cancers of the tonsil (57 years)
• Incidence of tongue and tonsilar malignancies increasing in several countries compared to decreases in other oral cancers over same timeframe

What’s the Fraction?

- Oropharyngeal cancers (OPC) attributable to HPV globally ~26%
  - More developed countries (North America, Japan, Australia): ~50%
- Inversely correlates with rates of smoking in the population
- Contributes more to OPC in men than women
- HPV 16: >80% of HPV positive OPCs


Risk Factors for HPV-Head and Neck Squamous Cell Carcinoma (HNSCC)

• Young age
• More likely to have higher SES
• More likely to have higher education
• More likely to have more lifetime sexual partners
• Associated with white race
• More likely to be diagnosed at later stage though survival better

Figure 1. Prevalence of Oral HPV Infection by Individual Genotypes in the US Population Aged 14 to 69 Years

The weighted prevalence (and 95% CI) for each of the 37 human papillomavirus (HPV) types evaluated is stratified by classification as high-risk or low-risk HPV types based on epidemiological associations with cervical cancer. HPV type 64 was not detected. The data are derived from the 5501 NHANES participants with evaluable samples. Error bars indicate 95% CIs.

Overall prevalence 6.9% (3.7% HR and 3.1% LR)!!; Gillison ML. JAMA 2012; 307: 693-703
Oral HPV prevalence and incidence

- Male university students (18-25yo), non-HIV infected, sexually active with women:
  - Prevalence oral HPV at enrollment – 7.5%
  - 12mo cumulative incidence – 12.3% (95% CI 7.0-21.3)
  - Prevalence HPV-16 – 2.8%
  - 12mo cumulative incidence HPV-16 – 0.8% (95% CI 0.1-5.7%)
  - None of the incident and 28.6% of prevalent oral HPV detected more than once

Factors Independently Associated with Oral HPV Infection:

- Age – bimodal distribution for men with peak prevalence 55-64yrs
- Sex – Males 3-fold higher than females
- Lifetime # sex partners – vaginal or oral sex
- Current smoking intensity – for F>M
Prevalence of Cervical and Oral Human Papillomavirus Infections Among US Women

- NHANES 2009-2010
- Prevalence of HPV infection among women 42.7% in the cervix and 3.8% in the oral cavity
- Prevalence of oral HPV 5-fold higher in women with cervical HPV compared to women without cervical HPV (7.0% vs 1.4%; PR 4.9; 95% CI 2.7-8.7)

Steinau M et al, JID 2014; 209: 1739-43
Anal HPV Infection is Common

Chin-Hong, et. al. , The Journal of infectious diseases, 2004
Ostor, A.G. International journal of gynecological pathology, 1993
Hernandez, B.Y. et. al., Cancer epidemiology, biomarkers & prevention, 2005
ANAL DYSPLASIA IS COMMON

ANAL CANCER INCIDENCE: NA-ACCORD

- HIV positive MSM: 131
- HIV positive non-MSM: 46
- HIV positive Women: 30
- HIV negative men: 2

Anal Cancer Statistics

- 0.4% of all cancers diagnosed in the U.S. in 2014
- Anal Cancer rates have increased by ~2%/yr since the 1970’s
- Incidence of SCCA among men in general population (~0.8/100K) vs HIV-infected MSM (~70/100K)

NCI 2014; Chiao EY. Clin Infect Dis 2006;43:223-33
Risk Factors for Anal Cancer

- High risk HPV*****
- HIV infection
- Multiple sex partners
- Multiple HPV strains
- Smoking
- Immunosuppression

What do we know?

• Anal cancer survival significantly improved for patients who receive a diagnosis of local disease (5-year survival – 78%) vs regional disease (56%) vs distant disease (18%)

• We do not know the natural history of anal dysplasia

• We do not know if screening individuals with anal Pap smears lead to improved outcomes

Chiao EY. Clin Infect Dis 2006;43:223-33
Conclusion

• Orientation ≠ Behavior
  – Ask

• Extragenital sexual activity is very common
  – Test

• Most STIs are asymptomatic
  – Treat

• HPV is ubiquitous and common in several non-cervical locations
Questions?