Sexually Transmitted Infections: Gonorrhea, Chlamydia, Trichomoniasis, and Human Papillomavirus

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Learning Objectives
After attending this presentation, learners will be able to:

▪ Describe the current epidemiology of the most common STIs
▪ Identify current treatment recommendations for gonorrhea, chlamydia, trichomoniasis
▪ Describe the current trends in gonococcal antimicrobial resistance

STIs are on the rise in the US

Limitations of case report data:
▪ Not all STDs are nationally notifiable (HPV)
▪ Most STDs are asymptomatic, only those diagnosed can be reported
▪ Trends are influenced by screening coverage and reporting practices

The STATE of STDs in the United States

1.7 million cases of Chlamydia
22% increase since 2013

555,608 cases of Gonorrhea
67% increase since 2013

30,644 cases of Syphilis
70% increase since 2013
Proportion* of MSM Attending STD Clinics with Primary and Secondary Syphilis†, Urogenital Gonorrhea, or Urogenital Chlamydia by HIV Status‡, STD Surveillance Network (SSuN), 2017

- 10-12 State Health Departments (SSuN)
- Visit level data
- Enhanced case data
- Common protocols

STI Testing during HIV care

- Initial care visit
  - Syphilis serology
  - NAAT (gonorrhea, chlamydia)
  - MSM (rectum, pharynx, urethra)
  - Hepatitis A, B, C
  - Women: Cervical pap test (HIV OI guidelines)
  - Trichomonas (NAAT)
  - Screening dependent on risk (3-6 mos)
    - New sex partner, partner with concurrent partners or more than one partner, or partner with an STI
    - High risk behavior
    - Partner services, prevention counseling

What about Rectal GC/CT Screening for women?

- 5499 women rectal CT/GC tests + other sites rectal positivity 10.8%
- ~ ⅊ have GC/CT had a rectal infection only

Women with rectal GC/CT rectum were more likely to have genital or pharyngeal GC/CT
During 2012–2017, the rates of reported GC increased:
- 112% among males
- 40% among females

Estimated Proportion* of MSM, MSW, and Women Among Gonorrhea Cases by Jurisdiction, STD Surveillance Network (SSuN), 2017

* Estimate based on weighted analysis of data obtained from interviews (n=6,409) conducted among a random sample of reported gonorrhea cases during January to December 2017.
† California data exclude San Francisco (shown separately).
Gonorrhea Clinical Manifestations

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Asymptomatic, Nasopharyngitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Asymptomatic, Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervicitis</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Subpharyngitis/Pelvic Inflammatory Disease</td>
</tr>
<tr>
<td>Urethra</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Epididymis</td>
<td>Epididymitis</td>
</tr>
<tr>
<td>Pharynx</td>
<td>Asymptomatic, Pharyngitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
</tbody>
</table>

Clinical Case—ARS Question 1

- 23 yo female G4P1
- Ankle swelling, pain, migratory polyarthritis, skin lesion left finger

What is the best method to make a diagnosis of DGI?

1. Joint aspiration
2. Blood culture
3. Lesion aspiration
4. Vaginal swab

Disseminated Gonococcal Infection (DGI)

- Estimated to account for 0.5-3% of gonococcal infections
- Risk factors: female, menses, pregnancy, terminal complement deficiency
- Clinical presentation
  - Monoarticular arthritis
  - Skin lesions (petechial or pustular) + tenosynovitis + polyarthritis
  - Perihepatitis, endocarditis, meningitis
- +Blood cx tenosynovitis/arthralgia > monoarticular arthritis
- Mucosal site infection often asymptomatic (NAAT)
- Antimicrobial susceptibility (AST) testing (culture)
Changing Patterns of DGI

DGI Cases by Site in ABCs, 2015 – 2017

- Demographics: 42% female, MSW 15.4%, Male 38%
- 30% >45 yrs

<table>
<thead>
<tr>
<th>Site</th>
<th>CA</th>
<th>GA-DPH*</th>
<th>GA-MSA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARS</td>
<td>1 / 1</td>
<td>6 / 770</td>
<td>21 / 29,323</td>
<td>26 / 68,730</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surveillance Area</th>
<th>CA</th>
<th>GA-DPH*</th>
<th>GA-MSA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 / 29,637</td>
<td>(0.007%)</td>
<td>3 / 9,770</td>
<td>(0.031%)</td>
</tr>
<tr>
<td></td>
<td>21 / 29,323</td>
<td>(0.072%)</td>
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</tbody>
</table>

Total 26 / 68,730 (0.0385)

Neisseria gonorrhoeae — Percentage of Isolates with Elevated Azithromycin Minimum Inhibitory Concentrations (MICs) (≥2.0 µg/ml), Elevated Ceftriaxone MICs (≥0.125 µg/ml), and Elevated Cefixime MICs (≥0.25 µg/ml), Gonococcal Isolate Surveillance Project (GISP), 2008–2017

- Percentage of Isolates with Elevated Azithromycin MICs and Elevated Ceftriaxone MICs with Other Resistance Phenotypes, GISP, 2017

- Azithromycin-RS=reduced azithromycin susceptibility (MIC ≥2 µg/ml); ceftriaxone-RS=reduced ceftriaxone susceptibility (MIC ≥0.125 µg/ml)

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<tbody>
<tr>
<td>AZI</td>
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<tr>
<td>MSM</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>MSW</td>
<td></td>
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</tr>
</tbody>
</table>

AZI 2017
MSM 7%
MSW 3%
MIC 2
Gonorrhea

- United States
  - Ceftriaxone 250 mg IM in a single dose PLUS Azithromycin 1 g orally in a single dose
- United Kingdom
  - Ceftriaxone 1 gram IM in a single dose
- Europe [European CDC]
  - Ceftriaxone 500 mg IM in single dose PLUS Azithromycin 2 gm orally in a single dose
- Japan
  - Ceftriaxone 1 gm IV/IM in a single dose

- Optimize therapeutic regimen
- PK/PD (site of penetration)
- Concentration dependent vs independent regimen
- Bacterial burden
- Mutational frequency to resistance
- Resistance suppressive targets do not guarantee eradication
- Novel agents (Zoliflodacin, Gepotidacin)

- Treatment Failures
- Most apparent treatment failure likely due to reinfection
- If treatment failure suspect, obtain culture/susceptibility test + ensure partner treatment
- Dual therapy in UK [Fifer 2016]
- Ceftriaxone MIC of 0.5mg/L, azithromycin MIC of >256mg/L in UK, Australia (March 2018)

Global Antibiotic Research and Development Partnership

- Launched by WHO and Drugs for Neglected Disease Initiative in 2016
- Draft of acceptable GC target product profiles and timeline
- Research and Development plan
  - Accelerate the development of a new clinical entity
  - Evaluate the potential of existing antimicrobials and combinations
  - Explore co-packaging and fixed dose combinations
  - Development of simplified treatment guidelines

Chlamydia
Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2017

![Graph showing rates of reported chlamydia cases by sex, United States, 2000–2017.]


![Bar chart showing prevalence of chlamydia by sex, race, Hispanic ethnicity, and age group, United States, 2013–2016.]

LGV inguinal syndrome

- *C. trachomatis* L1, L2, L3
- Herpetiform genital ulcers and/or papules
- Tender, fluctuant, inguinal lymphadenopathy (buboes)
**LGV Proctitis**
- MSM and women – rectal chlamydia NAAT
  - PCR based genotyping
  - Protocolitis +/- perianal ulcers
  - Presumptive tx (doxy 100 mg bid x 21 d)
  - Painful perianal ulcers or mucosal ulcers presumptive therapy for HSV
  - Short course therapy 7-14 d
  - GUM clinic in UK (Simon, STD 2018)

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**Notes from the Field Cluster of Lymphogranuloma Venereum Cases Among Men Who Have Sex with Men – Michigan, August 2015–April 2016**

- 38 reports of LGV among MSM with HIV infection
- Median age 26 (19-60), median CD4 483 (270-1271)
- 21/38 confirmed by CDC (19 symptomatic proctitis, 2 penile ulcer)
- Concomitant infections
  - 6/38 (16%) incident HIV
  - 4/38 (11%) hepatitis C
  - 6/38 (16%) syphilis
  - 8/38 gonorrhea (8% oral, 13% rectal)

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**LGV in MSM, NYC Sexual Health Clinics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>363</td>
<td>138</td>
<td>141</td>
<td>174</td>
</tr>
<tr>
<td>HIV positive</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>CD4 (cells/µL)</td>
<td>298</td>
<td>298</td>
<td>298</td>
<td>298</td>
</tr>
<tr>
<td>Concomitant infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>31%</td>
<td>31%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>syphilis</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>gonorrhea</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Chlamydia Treatment

- Azithromycin vs Doxycycline
  - Meta-analysis (Kong 2014)
  - Doxy > Azi 3% (urogenital)
  - Doxy > Azi 7% (sex urogenital)
- Rectal Infection
  - Several retrospective studies (doxy > azi)
  - STI CTU RCT Azi vs Doxy (aica)
- LGV
  - Azo vs sx (duration of therapy)
  - Reinfection is common
  - Retest in 3 mo

Human Papillomavirus

### HPV Natural History
- HPV is the most common STI
  - The majority of sexually active people will become infected
  - Initially most persons have no symptoms
  - Anogenital warts, low-risk (LR) HPV rarely cause cancer
- High-risk (16, 18) HPV infection may cause anogenital and oropharyngeal cancer
  - Most high risk HPV infection clears within 2 years
  - Minority develop high-grade squamous intra-epithelial lesions
  - HSIL can progress to cervical cancer 1/80 per year
Sexual Preference and HIV Infection Strong Independent Predictors of Male Anal HPV16


Oropharyngeal Cancer is the most common HPV associated cancer
Anal Cancer:
Increased 2.1%/yr male and 2.9%/yr female

Increased 2.7%/yr male and 0.8%/yr female
**HPV Vaccine**

**Nanovalent HPV Vaccine**
- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA approved to prevent warts, cervical, vulvar, vaginal and anal cancer
  - 2 doses for males/females aged 9-14
  - 3 doses for males/females aged 15-26
  - Immunocompromised patients need 3 doses, regardless of age of initiation
Vaccinating females leads to substantial herd protection from HPV in heterosexual men.

Proportion of Australian-born heterosexual men attending sexual health clinics with genital warts by age group, 2004-2011

HPV Vaccination in Gay, Bisexual Men

Proportion of Australian-born GBM attending sexual health clinics with anogenital warts, 2004-11

HPV Vaccination, Gay and Bisexual Men, 18-26yo

- The genoprotective efficacy population consisted of participants who were serosurveyed and had HPV DNA-negative warts and longer intervals on day 1 for recent vaccine types, were negative for oncogenic type DNA through month 7, and did not have any protocol violations. To document...
HPV Vaccination in HIV+ Adults >27 yrs

<table>
<thead>
<tr>
<th>Event</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Efficacy (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination infection</td>
<td>35</td>
<td>31</td>
<td>32% (1% to 64%)</td>
</tr>
<tr>
<td>Throat/tonsil infection</td>
<td>25</td>
<td>23</td>
<td>31% (1% to 64%)</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td>277</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>35</td>
<td>31</td>
<td>60% (4% to 94%)</td>
</tr>
<tr>
<td>Persistent infection</td>
<td>210</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Regression effect</td>
<td>210</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Anal Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does Treating HSIL Prevent Anal Cancer?

- **Anchor Study**
  - Assessment of anal HSIL treatment in reducing anal cancer in HIV+ men/ women vs active monitoring: digital anorectal exam
  - Ablative therapies: infrared coagulation, electrocautery, and TCA
  - Estimated recruitment > 5000, 5 year follow up
  - Patients randomly assigned to treatment or active monitoring arms
  - Estimated completion mid 2022

Trichomonas
Trichomonas vaginalis

- Single-celled protozoan parasite
- Adheres to epithelial cells
  - Male or female urethra
  - Female vagina, vulva
- Causes local inflammation
- Variable spectrum of disease
  - 70–85% of women and 77% of men are asymptomatic
  - Vaginitis, urethritis, prostatitis
  - Associated with increased susceptibility to other STIs (HIV), adverse pregnancy outcomes, low birth weight

T. vaginalis Epidemiology

<table>
<thead>
<tr>
<th>Add Health</th>
<th>NHANES</th>
<th>STD Clinics</th>
<th>Incarcerated</th>
<th>Drug Use</th>
<th>Patel, CID 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9%</td>
<td>3.1%</td>
<td>6.0%</td>
<td>8.6%</td>
<td>17.2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female Sex</th>
<th>Black Race</th>
<th>Older Age</th>
<th>&lt; High School</th>
<th>Below Poverty</th>
<th>&gt; 2 sexual Partners/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.0%</td>
<td>38.0%</td>
<td>26.0%</td>
<td>13.0%</td>
<td>26.0%</td>
<td>38.0%</td>
</tr>
</tbody>
</table>

Table 1. Comparative Prevalence of Sexually Transmitted Infections in the General, Noninstitrated US Population Ages 18–30 Years

<table>
<thead>
<tr>
<th>Infection</th>
<th>Prevalence, % (95% CI)</th>
<th>Crude</th>
<th>Adjusted (95% CI)</th>
<th>Adjusted (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV infection</td>
<td>Female</td>
<td>Male</td>
<td>Other Races/Countries</td>
<td>Female</td>
</tr>
<tr>
<td>TV infection</td>
<td>1.0 (0.7–1.3)</td>
<td>3.0 (2.4–3.8)</td>
<td>2.0 (1.6–2.4)</td>
<td>2.0 (1.6–2.4)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1.5 (1.3–1.7)</td>
<td>1.5 (1.3–1.7)</td>
<td>1.5 (1.3–1.7)</td>
<td>1.5 (1.3–1.7)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
</tbody>
</table>

National Harbor, Maryland, December 9-11, 2018
Trichomonas vaginalis and HIV acquisition

Forest plot of estimates of association between trichomoniasis and HIV acquisition

TV increased risk of HIV 1.5X

Masha, STI 2018

Trichomonas

- Screen at initial visit HIV+ (NAAT)
- Rx: Metronidazole HIV+ 500 mg bid x 7 days (Kissinger, 1999)
- Options to Nitroimidazoles
  - Single agent vs Combination therapy
  - Intravaginal: paromomycin, boric acid
  - Secnidazole
- Clinical treatment failure
  - Re-infection, Nonadherence
  - Antimicrobial resistance

- Retesting 3 months after treatment
- Management of persistent infection
  - Up to 17% at 3 months
  - Reinfection from untreated partner is common
  - Infection with M12-resistant strain: ~4-10%
  - Tinidazole-resistant ~1%
  - No clear relationship to clinical treatment failure
  - Susceptibility testing if resistance suspected (CDC)

STI Screening and Management

www.cdc.gov/std/tg2015
National Network of STD Clinical Prevention Training Centers (NNPTC)

- Clinical Training and Consultation Network
  - Visit: www.STDCCN.org
- Resources and tools for STD treatment
- STD Clinical Toolbox App
- Visit: www.nnptc.org

National STD Curriculum

- www.std.uw.edu
- Self-Study Modules
- Modular learning
- Free continuing education credits (CME and CNE)

Question-and-Answer
Sexually Transmitted Infections: Gonorrhea, Chlamydia, Trichomoniasis, and Human Papillomavirus

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SUGGESTED READINGS


