Sexually Transmitted Infections on the Rise: Syphilis, Chlamydia, and Gonorrhea

Kimberly A. Workowski, MD
Professor of Medicine
Emory University School of Medicine
Atlanta, Georgia

Financial Relationships With Commercial Entities
Dr Workowski has received grant support from GlaxoSmithKline. (Updated 11/22/19)

Learning Objectives
After attending this presentation, learners will be able to:
• Describe the increases in bacterial sexually transmitted infections (STIs)
• Identify unusual presentations of chlamydia and syphilis
• Discuss forthcoming changes in treatment recommendations
**Limitations of case report data**
- Not all STIs are nationally notifiable
- Most STIs are asymptomatic, only those diagnosed can be reported
- Trends are influenced by screening coverage and reporting practices

**STIs are on the rise**

The State of STDs in the United States

STS SURGE FOR THE FIFTH STRAIGHT YEAR REACHING AN ALL-TIME HIGH.

1.8 million CASES OF CHLAMYDIA
10% case decline since 2014

583,405 CASES OF GONORRHEA
60% case increase since 2014

115,045 CASES OF SYphilis
71% case increase of bedestet syphilis since 2014

1,306 CASES OF SYPHILIS AMONG NEWBORNS
100% case increase since 2014

**Proportion of MSM Attending STD Clinics with Primary and Secondary Syphilis, Urogenital Gonorrhea, or Urogenital Chlamydia by Known HIV Status, STD Surveillance Network (SSuN), 2018**

**STI Screening**

**Women and Heterosexual Men**
- Chlamydia, Gonorrhea
- Women <25 or older women (increased risk) annually
- Self collected vaginal swab
- No extragenital testing
- HIV (thymonoma, pap smear)
- Heterosexual men
- Consider chlamydia screening (adolescents, nonhomosexual, STD clinic)
- Population based gonorrhea screening not recommended
- No extragenital testing
- Retest 3 mo after treatment

**Men who Have Sex with Men**
- HIV Ag/Ab serology
- Syphilis serology (RPR/treponemal)
- Chlamydia, Gonorrhea
- Urethral infection (NAAT)
- Rectal infection (NAAT)
- Pharyngeal infection gonorrhea (NAAT)
- Hepatitis A, B
- Hepatitis C (MSM/HIV)

At least 1 yr, qtrly or more based on risk
### Rectal Gonorrhea

<table>
<thead>
<tr>
<th>Source</th>
<th>Rectal Gonorrhea</th>
<th>Rectal Chlamydia</th>
<th>Pharyngeal Gonorrhea</th>
<th>Pharyngeal Chlamydia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al 2016</td>
<td>0.20% - 24.0%</td>
<td>2.1% - 23.0%</td>
<td>0 - 16.5%</td>
<td>0 - 3.6%</td>
</tr>
<tr>
<td>Dewert et al 2018</td>
<td>6.1% (weighted average)</td>
<td>9.0% (weighted average)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHBS MSM 2017</td>
<td>3.6%</td>
<td>7.9%</td>
<td>4.6%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### ARS Question #1: 49 yo male HIV+, DM, CKD, CVA, HBV, HDV

- Lip pain, weight loss, anorexia, dysphagia
- CD4 453, HIV VL 275,000, HBV VL 177,000,000, CK 2

**Diagnostic testing?**

A) Darkfield microscopy  
B) HSV PCR  
C) Treponemal EIA  
D) Chlamydia/GC  
E) RPR

### Syphilis
Syphilis Continues to Increase

Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners and HIV Status, United States, 2018

Proportion of P&S Syphilis Cases that Reported Meth or Heroin Use or Sex with a PWID, 2012–2016
Public Health Implications

CDC Call to Action
Let’s Work Together to Slay the Tide of Rising Syphilis in the United States

- Two epidemics
  - MSM networks
  - Heterosexual networks
- Historic success in heterosexual epidemics
  - Intensive partner services, contact tracing
  - Targeted community outreach, screening, treatment to reach at-risk individuals
- Less success addressing MSM epidemics
  - MSM in smaller metropolitan areas and Southwest and Midwest more commonly linked to heterosexual women and less likely to identify (Oster, STD, 2014)

Primary Syphilis

- Chancre appears 10-90 days after infection
  - Single, painless, indurated, with rolled edges
  - Multiple or persistent lesions
  - Most are asymptomatic
- Regional adenopathy (painless)
- Primary urethritis

Secondary Syphilis

- ~3-6 weeks after primary
  - Rash
    - Generalized lymphadenopathy
    - Constitutional symptoms
  - Mucous patches
  - Condylomata lata
  - Patchy alopecia

Public Health Implications

Primary Syphilis

- Chancre appears 10-90 days after infection
  - Single, painless, indurated, with rolled edges
  - Multiple or persistent lesions
  - Most are asymptomatic
- Regional adenopathy (painless)
- Primary urethritis

Secondary Syphilis

- ~3-6 weeks after primary
  - Rash
    - Generalized lymphadenopathy
    - Constitutional symptoms
  - Mucous patches
  - Condylomata lata
  - Patchy alopecia
Unusual presentations

- *T. pallidum* PCR+ 1° anogenital lesions (Thomas et al. 2016)
- Anal lesions were more common in HIV+ (34.2%) vs. HIV- (11.6%).
- 49.2% of 1° anal or genital lesions were painful, 37.7% were multiple. Of n=37 with painful and multiple lesions, only 8% had concurrent HIV.

<table>
<thead>
<tr>
<th>Table 1: <em>Clinical characteristics of hepatitis-pallidum</em> 1° anogenital syphilis lesions among men by HIV status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive (n=37)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female or mixed</td>
</tr>
<tr>
<td>Single lesion</td>
</tr>
<tr>
<td>Multiple lesion</td>
</tr>
<tr>
<td>Painful</td>
</tr>
<tr>
<td>Multiple</td>
</tr>
</tbody>
</table>

MMWR 60(5);2011

Syphilis serologic screening algorithms

**Traditional**
- RPR (Sensitivity)
  - Primary: 62-78%
  - Secondary: 97-100%
  - Tertiary: 47-64%

**Reverse sequence**
- Early primary, requires RPR (active), false +
- Active infection, Fs, miss early
Can enhanced screening impact syphilis rates?

- Screening of MSM populations at increased risk for syphilis is suboptimal.
- Increased screening of MSM may be reducing infectious (primary and secondary) syphilis (Australia).
- More frequent screening (q3 to 6mo) of high risk MSM was more cost effective than increased screening coverage in controlling incident syphilis (modeling).

**Evaluation of CNS Involvement**

- Initial spirochetal invasion during early syphilis
  - Resolve or progress
  - Neurologic symptoms/signs
  - CSF examination
    - Auditory disease, cranial nerve dysfunction, meningitis, stroke, altered mental status, loss of vibration, iritis, uveitis Neurologic or ophthalmic symptoms/signs
    - Tertiary disease
      - aortitis, gumma
    - Serologic treatment failure
  - CNS invasion in early syphilis is common
  - CSF abnormalities of unclear significance in the absence of signs/symptoms
  - Neurosyphilis = CSF tests + reactive RPR + signs/symptoms
Ocular Syphilis

- Every part of the eye can be involved during any stage of the infection
- Secondary syphilis or late stage
- Serologic tests +
  - Late ocular syphilis, 90% NEGATIVE serum RPR but + treponemal test
  - Rarely, early syphilis (primary stage) negative treponemal and RPR + eye
- 30-40% of persons with ocular syphilis will have a normal CSF examination

Cardiovascular Syphilis

- Aortitis (thoracic aorta)
  - Endarteritis obliterans vasa vasorum
  - Disruption of media - dilation
  - Aortic regurgitation
  - Surgical evaluation for symptoms or diameter > 5.5 cm
  - Rupture may occur in 15-30% of cases
  - 47-year-old HIV+ man VL <10
  - 10 years after secondary syphilis; RPR 1:1, TPPA +
  - + wide pulse pressure, systolic and diastolic murmur
  - Echo - moderate to severe AR
  - 6.8-cm fusiform aneurysm proximal aorta.
  - Histology - inflammation with plasma cells, gummas/histiocytes/giant cells with calcified plaques.

ARS #2: 32 yo HIV + man on arvs (VL <20) with sore throat, blurry vision. +anterior uveitis, RPR 1:128, LP (nl protein, glucose, VDRL neg)

Treatment Options:

A) Benzathine PCN 2.4 mu IM x1
B) Benzathine PCN 2.4 MU IM X 3 wkly
C) Penicillin G 24 mu IV daily x 14 days
D) Doxycycline 100 mg bid x 14 days
E) Amoxicillin 3 grams daily + probenecid 500 mg qid x 14 days
Syphilis Treatment

- Benz Pen 2.4 mu IM x 1 early syphilis
- Role of enhanced therapy
  - Rolfs 1997
  - Observational > 500 HIV+: no difference in serologic outcomes at 12 months 1 vs 3 (Rome 2016, Feng 2016)
  - Andrade R et al. CID 2017, RCT, 64 HIV+ patients with early syphilis
    - IM+oral vs IM alone
    - RCT Beno pen 1 vs 3 early syphilis (NCT 0057060)
- PCN alternatives (early, latent, NS)
  - Doxycycline (6 observational)
  - Ceftriaxone 1 g x 10d, HIV+ (Cas, CID 2017)

Monitoring

- Serologic nonresponse: lack of a four fold decline in nontreponemal antibody titers 12 (Early) or 24 (Late) months after therapy depending on the stage of syphilis
- Nontreponemal test titers might decline more slowly for persons previously treated for syphilis
- Serologic associated with several factors
  - Stage of syphilis
  - Initial nontreponemal titers
  - Age (older patients less likely to decline fourfold)

STI PEP/PrEP with Doxycycline

Bolan RK, STD 2015
- 30 HIV+ MSM ≥2 episodes syphilis
- Doxycycline PEP 100mg po daily x 36 weeks (N=15) vs. incentive based STI-free (N=15)
- Doxycycline PEP decreased risk of incident syphilis, GC or CT (OR: 0.27, CI: 0.09-0.38).

Molina, Lancet ID 2018
- 23 HIV-high risk MSM (IPERGAY)
- Doxycycline PEP 200mg 24-72 hours after high risk sex (n=116) vs. no PEP (n=116)
- Doxycycline PEP associated with lower occurrence of first episode of syphilis (HR 0.27, CI: 0.07-0.98), followed: median 8.7 mos.
- Five studies underway or in development (Canada, Australia, France, United States)
- Concerns and challenges
  - Efficacy not determined, small sample sizes
  - Which MSM would benefit most?
  - Risk compensation
  - Dose, regimen, and formulation (monohydrate versus hyclate)
  - Effect on microbiome
  - Antimicrobial resistance (23% GC resistance)
Chlamydia

Chlamydia — Proportion of STD Clinic Patients Testing Positive by Age Group and Sex and Sex of Sex Partners, STD Surveillance Network (SSuN), 2018

Chlamydia & Gonorrhea Diagnostic Tests
- Nucleic acid amplification tests (NAAT) recommended for women & men
- Optimal specimen: vaginal swabs in women and first-catch urine in men
- NAAT optimal for rectal and pharyngeal testing (MSM)
  - recently FDA approved at extragenital sites
- Limitations: no antibiotic resistance testing with NAAT
- NAAT POC tests

http://www.cdc.gov/mmwr

Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014
Chlamydia Treatment

- **Azithromycin vs Doxycycline**
  - RCT data: CT urethritis treatment with azithro has a cure rate of <95% (Schwebke, Manhart, Kissinger, Geisler)
  - Meta-analysis (Kong 2014)
    - Doxy > Azi 3% (urogential)
    - Doxy > Azi 7% (ux urethral)
- **Rectal Infection**
  - Several retrospective studies (doxy=az)
  - Retest in 3mo (reinfection)

---

Chlamydia Treatment

- **Doxy is highly efficacious - all sites in men and women**
- **Azithromycin**
  - efficacious in women and asymptomatic men
  - lower efficacy in urethritis, poor efficacy in rectum, 7pharynx
- **RCT** (asymptomatic) - US, UK, Australia
- **CDC Guidelines** Draft recommendations
  - Doxycycline 100 mg bid
  - Azithromycin 1 gram alternative regimen

---

**LGV Inguinal syndrome**

*Ch. trachomatis* L1, L2, L3

Herpetiform genital ulcers and/or papules
Tender, fluctuant, inguinal lymphadenopathy (buboes)
LGV Proctitis

Proctocolitis in MSM or GUD + tender inguinal lymphadenopathy +/- 1 perianal ulcers
- Compatible clinical syndrome
- + CT test at the anatomic site
- Exclusion of HSV, gonorrhea, syphilis
- Genotyping LGV

Tx: Doxycycline 100 mg bid x 21 d (meta-analysis: 98.5% cure)
- Short course therapy 7-14 d GUM clinic in UK (Simon, STD 2018)
- Empiric tx for HSV + ulcers
- Asymptomatic infection can occur

How likely is a patient with proctitis to have LGV?

- No routine surveillance in U.S.
- 2 studies of patients with anorectal symptoms and + CT
  - NYC, 2012-15: 23% had +LGV PCR
  - San Francisco, 2016-18: 48% had +LGV PCR
- Epi associations: HIV+, older age, Black or Hispanic
- Clinical characteristics: anal discharge, bleeding, >=10 WBC on rectal gram stain
- Asymptomatic infection can occur
  - Wide range in European studies (10-90%)
  - NYC, 2012-15: 6% of ax CT cases had +LGV PCR
  - Treatment ax infection doxy bid x 7 d as well as partners <60 days

Diagnostic testing?

A) Darkfield microscopy
B) HSV PCR
C) Treponemal EIA
D) Chlamydia/GC
E) RPR

Evaluation:
- HIV, DL, HSV ax, HSV serology +, CT
- Empiric tx with doxy + valtrex
- Ulcer + CT with genotyping L2b
  - 7 published cases
  - Chandrasekar, Emerg Inf Dis 2019
  - 25 MSM (4 + JCD 73, V1 300,000)
  - >30 oral sex partners
  - patchy ulcers, adenopathy
  - Ulcer + CT with genotyping L2b
Gonorrhea

Gonorrhea — Rates of Reported Cases by Sex, US, 2009–2018

Gonorrhea Clinical Manifestations

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</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, pharyngitis</td>
</tr>
<tr>
<td>Rectum</td>
<td>Asymptomatic, Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic (i.e., joint, blood, other sterile site)</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervicitis</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Salpingitis/Pelvic Inflammatory Disease (PID)</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>Asymptomatic, Proctitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Systemic (i.e., joint, blood, other sterile site)</td>
<td>Disseminated Gonococcal Infection (DGI)</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
</tr>
<tr>
<td>Pharynx</td>
<td>Asymptomatic, pharyngitis</td>
</tr>
<tr>
<td>Eye</td>
<td>Conjunctivitis (Neonatal Ophthalmia)</td>
</tr>
</tbody>
</table>
Disseminated Gonococcal Infection (DGI)

- 0.5–3% of gonococcal infections
- Risk factors: female/menses/pregnancy, terminal complement deficiency
- Clinical presentation
  - Monoarticular septic arthritis
  - Skin lesions (petechial or pustular) + tenosynovitis + polyarthralgia
  - Pericarditis, endocarditis, meningitis
  - Mucosal site asymptomatic (NAAT)
- Antimicrobial susceptibility (AST) culture
- DGI Infection associated with eculizumab
  - FDA adverse event reporting system (June 2018)

Changing Patterns of DGI

DGI Cases Surveillance, 2015 – 2018

- GC Sterile site isolate (CA, GA)
- 2015-16 (retrospective); 2017-prospective
- 52 cases
- Demographics: 59% male (MSM 16%), 15–29 yo (34%), >45yr (34%)
- 25% septic arthritis
- 13% HIV+
- Underestimate of true burden of DGI
  - Surveillance area ~4% of US population

Neisseria gonorrhoeae — GISP, 2000–2018

Figure 29. Neisseria gonorrhoeae — Percentage of Isolates with Elevated Minimum Inhibitory Concentration (MIC) to Azithromycin, Ceftriaxone, and Ciprofloxacin, Gonococcal Isolate Surveillance Project (GISP), 2000–2018

Figure 31. Neisseria gonorrhoeae — Prevalence of Tetracycline, Penicillin, or Ciprofloxacin Resistance or Elevated Concentration of Azithromycin, Ceftriaxone, or Ciprofloxacin among Gonococcal Isolate Surveillance Project (GISP) Isolates, 2000–2018
Neisseria gonorrhoeae — Percentage of Urethral Isolates with Elevated Minimum Inhibitory Concentrations (MICs) to Azithromycin* and Ceftriaxone† by Sex and Sex of Sex Partners, Gonococcal Isolate Surveillance Project (GISP), 2009–2018

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
  - Ceftraxone 1 gm IV/IM in a single dose

Optimize therapeutic regimen
- PK/PD, bacterial burden
- Treatment Failures
- Reinfection
- Culture/AST + partner treatment
- Novel Agents (Zoliflodacin, Gepotidacin)
- WGS for genomic epidemiology
- Identification of mutations conferring resistance
- Characterizing outbreaks and spread of resistant strains

GC Treatment Draft Recommendations
Ceftriaxone 500 mg IM once*
*for persons weighing 150 kg or more, use 1g IM Ceftriaxone

Anti-chlamydial therapy when chlamydia has not been ruled out
- Azithromycin resistance is widespread and increasing
- Wide inter-individual pharmacokinetics
- Resistance prevention concentration unknown, likely higher than dose for cure
- Pharyngeal gonorrhea is common/under-screened (test of cure 7-10 d)
STIs on the Rise

- Syphilis
  - Heterosexual, MSM
  - Painful ulcers, ocular, CV
  - Screen frequently
- Chlamydia
  - Extra-genital infection (MSM)
  - LGV oral and rectal
  - Doxycycline
- Gonorrhea
  - Resurgence of DGI
  - Antimicrobial resistance
  - Ceftriaxone
  - Pharynx test of cure

Acknowledgments
- 2020 Guidelines Development Committee
- Khalil Ghanem/Sue Tuddenham (Syphilis)
- William Geisler (CT)
- Lindley ReSev/Santa Syphilis

Question-and-Answer Period