Clinical Update: Sexually Transmitted Infections

2021 CDC STI Treatment Guidelines
Providence, Rhode Island
August 25th, 2021

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Disclosures

Funding from the National Institutes of Health (NIH) and the Rhode Island Department of Health.

No commercial conflicts of interest.
A 182% increase in new infectious syphilis cases over the last 10 years.

Cases of Infectious Syphilis
Rhode Island, 2011-2020*

*2020 data is preliminary
Cases of Gonorrhea
Rhode Island, 2011-2020*

A 288% increase in new gonorrhea diagnoses over the last 10 years

*2020 data is preliminary
Cases of Chlamydia
Rhode Island, 2011-2020*

A 14% increase in new chlamydia diagnoses over the last 10 years

*2020 data is preliminary
## Reported Cases of STDs by Month, 2019-2021*

*2020 data is preliminary; 2021 data is preliminary

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<th>Jan</th>
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### 2019 vs. 2020, Full Year:
- **CT:** 17% decline
- **GC:** 8% decline
- **IS:** 11% decline

### 2020 vs. 2021, January – June
- **CT:** 20% rebound
- **GC:** 47% rebound
- **IS:** 31% rebound
Overview
Prevention and Control of STIs

1. Risk assessment and education and counseling
   • Focus on sexual and gender minority groups
   • Five P’s (Partners, Practices, Protection, Past History, Pregnancy)

2. Pre-exposure vaccination for vaccine-preventable STIs
   • HPV (routine at 11-12 years, from 9-26 years, consider 27-45 years)
   • HAV/HBV for all adolescents and young adults
   • HAV/HBV (MSM, PWID, HIV, HCV, homeless)

3. Identification of people with asymptomatic and symptomatic infection

4. Effective diagnosis, treatment, counseling, and follow-up
   • PrEP for HIV and STIs
   • PEP for HIV and STIs

5. Evaluation, treatment and counseling of sex partners
Screening Recommendations
Special Populations

1. GC/CT screening annually for all sexually active females aged <25 years (Opt-out)
   • CT rectal testing and GC rectal and pharyngeal testing can be considered for females based on sexual behaviors
   • Insufficient evidence for screening among males based on efficacy and cost-effectiveness
   • Screening of young men in settings with a high prevalence (corrections, STI Clinics, etc.)

2. MSM: Annual screening for HIV, syphilis, and GC/CT (Urogenital and rectal testing based on sexual behaviors; GC pharyngeal testing; CT pharyngeal testing still not recommended; self swabbing acceptable)
   • More frequent STI screening (3-6 months) if multiple sex partners or other risks
   • PrEP: Screen for STIs at least every 6 months, every 3 months if ongoing risk
The Importance of Extragenital STD Testing

Over 70% of gonorrhea (GC) and chlamydia (CT) infections among MSM are missed by urogenital screening only.

Receptive anal sex can lead to rectal GC/CT infection that would be missed with urogenital screening only.

Performing oral sex can lead to pharyngeal GC/CT infection that would be missed with urogenital screening only.

Urogenital screening tests for the presence of GC/CT in the urethra.

"Don’t forget the triple dip!"

*Self-collected swabs are OKAY

Patton at al., CID, 2014
HIV Screening Recommendations

1. All people seeking STI evaluation
2. At least once for all persons aged 15-65 years (USPTF and CDC)
3. MSM: At least annually, every 3-6 months if increased risk
4. Opt-out approach
5. No need for a separate sign consent process
6. Antigen/Antibody recommended initial test
7. Confirmatory testing if initial test is positive
8. If unlikely to follow-up, consider point-of-care testing
9. HIV RNA PCR testing if concern for acute HIV
10. Assess eligibility for PrEP or PEP

STI Screening for People with HIV Infection: Screen for syphilis, GC, and CT at the initial visit and then at least annually. Includes extragenital GC/CT testing, and annual trichomonas screening for women. Every 3-6 month STI screening depending on risk behaviors.
Syphilis (Treponema pallidum)
Diagnostic Considerations

1. *T. pallidum* can infect the CNS at any stage including the visual (ocular syphilis) or auditory (otosyphilis) systems. Ocular and otosyphilis most common during early stages.

2. **Ocular syphilis:** Typically uveitis, but also conjunctivitis, keratitis, others. Can result in permanent vision loss.

3. **Otosyphilis:** Tinnitus, vertigo, sensorineural hearing loss (uni- or bilateral, potential sudden onset, progress rapidly). Can result in permanent hearing loss.

4. **Darkfield examination** is definitive diagnostic method (limited availability).

5. **Typical approach:** Serological testing with *two* tests (nontreponemal and a treponemal test). Use of one test is *insufficient* for diagnosis.
Traditional Testing Algorithm

*False positive nontreponemal tests can be associated with other infections (e.g. HIV), autoimmune conditions, vaccinations, pregnancy, and older age.

**Non-treponemal tests (e.g., RPR, VDRL)**
- NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

**Treponemal tests (e.g., TPPA, FTA-Abs)**
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME

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Reverse Sequence Testing Algorithm

*Newer treponemal screening tests: Enzyme immunoassays (EIA), Chemiluminescence immunoassays (CIA). Microbead immunoassays (MBIA)
Syphilis (Treponema pallidum)
Diagnostic Considerations

1. **Nontreponemal test antibody** titers can correlate with disease activity.
2. A **fourfold change** in titer indicates a clinically significant difference.
3. Use the **same** testing method (VDRL or RPR) and by the **same** laboratory. RPR titers frequently **slightly higher** than VDRL.
4. Nontreponemal antibodies may decrease **less** than fourfold after treatment (inadequate serologic response) or may decrease appropriately but **persist**.
5. 15-25% of **treponemal** tests may become nonreactive after 2-3 years in people treated during the primary stage.
6. **Treponemal antibody titers** do **not** correlate with treatment.
Syphilis (Treponema pallidum) 
Diagnostic Considerations

1. **CSF Evaluation** is warranted for any signs of neurosyphilis (CN dysfunction, meningitis, stroke, altered mental status).

2. Full ocular examination for ocular symptoms.

3. If isolated ocular symptoms, confirmed on examination, and positive serology, then CSF examination is unnecessary before treatment.

4. For isolated auditory abnormalities (otosyphilis) and positive serology, CSF evaluation is likely to be normal and unnecessary before treatment.

5. Diagnosis of neurosyphilis based on CSF cell count, protein, and CSF-VDRL (with positive serology and consistent signs/symptoms).

6. CSF-VDRL very specific, insensitive (i.e. a positive test is considered diagnostic, but a negative test does not rule it out).

7. Can consider CSF FTA-ABS (less specific, highly sensitive).
Syphilis Treatment

Early (Primary, Secondary, Latent less than one year): Benzathine penicillin 2.4 m.u. IM once

Late (Latent more than one year, cardiovascular, gummas): Benzathine penicillin 2.4 m.u. IM weekly for three weeks

Neurosyphilis: Penicillin G 3-4 m.u. IV every four hours or 24 m.u. continuous infusion for 10-14 days

Congenital: Penicillin G 50,000 units/kg every 8-12 hours for 10-14 days

*Pregnant with syphilis and allergic to penicillin: DESENSITIVE
*Repeat serologic testing at 6- and 12-months post-treatment (+24 months for latent syphilis, 3-, 6-, 9-, 12-, and 24-months for primary/secondary and 6-, 12-, 18- and 24- months for latent if HIV positive).
Successful treatment is a 4-fold decline in titers. More frequent follow-up prudent if concern for repeat infection. If concern for treatment failure, CSF examination is recommended.

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Alternative Syphilis Treatment (Penicillin Allergy)

Early (Primary, Secondary, Latent less than one year): Doxycycline 100mg PO BID for 14 days

Late (Latent more than one year, cardiovascular, gummas): Doxycycline 100mg PO BID for 28 days

Neurosyphilis: Ceftriaxone 1-2g IM or IV for 10-14 days (limited data)

*Pregnant with syphilis and allergic to penicillin: DESENSITIVE
# Syphilis Treatment Follow-up

<table>
<thead>
<tr>
<th>Early Syphilis</th>
<th>Latent Syphilis</th>
<th>Neurosyphilis</th>
<th>HIV positive</th>
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<tbody>
<tr>
<td>Follow-up 6- and 12-months</td>
<td>Follow-up 6- and 12- and 24-months</td>
<td>Repeat CSF examinations unnecessary if have an appropriate serologic and clinical response.</td>
<td>Follow-up at 3-, 6-, 9-, 12- and 24-months (primary or secondary); 6-, 12-, 18- and 24- months (latent).</td>
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</tbody>
</table>

If less than a fourfold decrease, no neurological findings and reinfection unlikely: Benzathine penicillin IM for three weeks, can consider CSF examination.

*Perform a CSF examination for any neurological findings

**10-20% of people with primary/secondary syphilis do not have a fourfold decrease in titer at 12 months
Management of Partners

- Exposed within 90 days to primary, secondary or early latent syphilis
  - Treat, even if seronegative
- Exposed >90 days to primary, secondary or early latent syphilis
  - Treat, if serologic test results not available immediately and follow-up is uncertain
- Exposed to late latent syphilis or syphilis of unknown duration
  - Evaluate clinically and serologically, treat if syphilis suspected
# Chlamydia Screening

Annual screening for all sexually active women age <25 years and for older women at increased risk (new sex partner, >1 partner, partner with >1 partner, partner with an STD)

*Rectal and oral NAAT’s are now FDA cleared. Rectal CT testing can be considered in females depending on sexual behavior and exposures.*

## Summary of Recommendations and Evidence

<table>
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<th>Population</th>
<th>Recommendation</th>
<th>Grade (What’s This?)</th>
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<td>Sexually Active Women</td>
<td>The USPSTF recommends screening for chlamydia in sexually active women age 24 years and younger and in older women who are at increased risk for infection.</td>
<td>B</td>
</tr>
<tr>
<td>Sexually Active Women</td>
<td>The USPSTF recommends screening for gonorrhea in sexually active women age 24 years and younger and in older women who are at increased risk for infection.</td>
<td>B</td>
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<tr>
<td>Sexually Active Men</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for chlamydia and gonorrhea in men.</td>
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_RHODE ISLAND DEPARTMENT OF HEALTH_
Chlamydia Treatment
Uncomplicated genital, rectal, or pharyngeal infections

**Recommended**: Doxycycline
100mg PO BID for seven days

**Alternative**: Azithromycin
1 gram PO once

Alternative regimens: Levofloxacin, Erythromycin, Ofloxacin
Chlamydia Treatment
Doxycycline versus Azithromycin

- **Meta-analysis of 23 studies** (Long et al., CID, 2014): Small increased efficacy of up to 3% for doxycycline compared with azithromycin for urogenital CT and 7% increased efficacy for doxycycline for symptomatic urethral CT treatment in men.

- **Cochrane Review of 14 studies** (Paez-Canro, 2019): “In men, regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure. For women, we are uncertain whether azithromycin compared to doxycycline increases the risk of microbiological failure.”

- **Observational studies**: Doxycycline is more efficacious for rectal C. trachomatis infection for men and women than azithromycin (Dukers-Muijrers, CID, 2019).

- **MSM**: RCT for the treatment of rectal CT among MSM reported microbiologic cure was 100% with doxycycline and 74% with azithromycin (Dombrowski, CID, 2021).

- **Other**: CT detected at the anorectal site among 33%–83% of women who had urogenital C. trachomatis infection, and its detection was not associated with report of receptive anorectal sexual activity (Dukers-Muijrers et al., BMC ID, 2015).
Chlamydia Treatment Considerations

1. Recent sex partners (within 60 days of symptoms) should be referred for evaluation (or last sex partner).
2. Once treated, individuals should abstain from sex for seven (7) days.
3. Retesting at three (3) months.
4. A test-of-cure at 4 weeks is not recommended (except in pregnancy).
5. HIV testing!
### Time to clearance of NAAT in Chlamydia Infection

<table>
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<th>Day after treatment (N=61)</th>
<th>% with negative NAAT</th>
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<tr>
<td>Day 0</td>
<td>0/61 (0%)</td>
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<tr>
<td>Day 3</td>
<td>7/61 (12%)</td>
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<tr>
<td>Day 7</td>
<td>28/61 (46%)</td>
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<tr>
<td>Day 14</td>
<td>48 (79%)</td>
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Linear regression predicted time to clearance: **17 days** (95%CI: 16-18 days)

*115 women with chlamydia treated with 1 gram of azithromycin, vaginal NAAT on day 0, 3, 7, 14*

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*Renault et al. Sex Health, 2011*
Lymphogranuloma Venereum (LGV) Considerations

1. Caused by *C. trachomatis* serovars L1, L2, or L3 (serovars A-K are mild/asymptomatic).

2. Clinical Presentation: Ulceration or papule (self-limited), lymphadenopathy (unilateral, inguinal or femoral), proctitis (mucoid/hemorrhagic rectal discharge, anal pain, tenesmus, constipation, fever). Can lead to colorectal fistulas and strictures. Reactive arthropathy.

3. Diagnosis: CT NAAT; LGV-specific molecular typing (available only from the CDC)

4. Treatment: Doxycycline 100mg PO BID for 21 days
Gonorrhea Screening
Genital, rectal, and pharyngeal infections

Annual screening for all sexually active women age <25 years and for older women at increased risk (new sex partner, >1 partner, partner with >1 partner, partner with an STD)
Gonorrhea Treatment
Uncomplicated genital, rectal, or pharyngeal infections

**Recommended:** Ceftriaxone 500mg IM once † (Monotherapy)

**If concern for chlamydia:**
Doxycycline 100mg PO BID x 7 days

*2015 CDC Guidelines:* Ceftriaxone 250mg IM once and azithromycin 1g PO once (regardless of chlamydia testing)

**Disseminated GC:** Ceftriaxone 1g IM or IV Q24 hours (Alternative: Cefotaxime or Ceftizoxime 1g IV Q 8 hours).

†Change made December 18, 2020, www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm
Gonorrhea Treatment
Uncomplicated genital, rectal, or pharyngeal infections

If ceftriaxone is unavailable, can do:

- Gentamicin 240mg IM + Azithromycin 2 grams PO once (3% vomiting)

  or

- Cefixime 800mg PO once
  (was 400mg PO once)

*Test-of-cure is not needed except for pharyngeal infections (re-test at 7-14 days) or if persistent symptoms (2015: Only re-test if alternative regimen used for pharyngeal infection).

**In penicillin allergic patients, can perform gyrase A testing to identify cipro susceptibility, and treat with cipro 500mg PO once if sensitive.
Gonorrhea Treatment

Why the Change?

1. **CDC’s 2010 Guidelines** recommended dual therapy with cephalosporin plus azithro/doxycycline due to concerns of resistance (cephalosporins only effective class)
2. **2006-2011**: Increasing cefixime MIC’s
3. **2012**: Cefixime no longer recommended as first-line.
4. **2013-Current**: GISP isolates with reduced azithromycin susceptibility increased tenfold (5.1% in 2019)
5. **Current**: Emerging azithromycin resistance in other pathogens (*M. genitalium*, *Shigella*, *Campylobacter*).
6. Almost all GC strains have been **susceptible** to ceftriaxone, cefixime, and azithromycin (GISP). A higher ceftriaxone dose recommended to overcome elevated MICs, especially in the oropharynx.
Gonorrhea Treatment Considerations

1. Recent sex partners (within 60 days of symptoms) should be referred for evaluation.
2. Once treated, individuals should abstain from sex for seven (7) days.
3. Retesting at three (3) months.
4. HIV testing!
5. Expedited partner therapy (EPT) with cefixime 800mg. “Shared decision making” regarding EPT and MSM.
Mycoplasma Genitalium

1. First identified in the 1980’s
2. Common cause of male urethritis (accounts for 15-25% of non-gonococcal urethritis in the United States)
3. In women, *M. genitalium* has been associated with cervicitis, PID, preterm delivery, spontaneous abortion, and infertility (twofold increase).
4. Difficult to culture (slow growing)
5. Commercially available NAAT (FDA cleared, Aptima)
Mycoplasma Genitalium

1. Rapidly increasing azithromycin resistance (44-90%).
2. Doxycycline is largely ineffective.
3. Moxifloxacin (400mg PO Daily for 7 days) has been shown to be effective in small studies, but emerging resistance (0-15%).
4. No commercially available resistance tests in the United States (yet).
Mycoplasma Genitalium

Who should be tested?

1. Men with recurrent urethritis.
2. Women with recurrent cervicitis.
3. Consider testing women with PID.
4. Testing should be accompanied by resistance testing if available (it’s not).
5. Screening of asymptomatic infection and extragenital testing is not recommended.
Mycoplasma Genitalium

Treatment

**Recommended:** Doxycycline 100mg PO BID for 7 days (reduces organism load and facilitates clearance)

**Followed by:** Moxifloxacin 400mg PO Daily for 7 days

*If resistance testing is available, and macrolide sensitive, could do:*
Doxycycline 100mg PO BID for 7 days followed by azithromycin 1g PO once and then 500mg PO daily for an additional three days.
Genital Herpes
Diagnostic Considerations

1. Both HSV-1 and HSV-2 can cause genital herpes
2. Diagnosis: NAAT or culture of genital lesions
3. HSV-1/2 IgM are not type specific and can be positive during recurrent genital or oral episodes of herpes, not recommended.
4. HSV-1/2 IgG develop during the first weeks of infection, can be (falsely) negative early in infection (re-test 12 weeks later if suspected). Some EIA tests (HerpeSelect) can be falsely positive at low index values, should confirm with another method.
5. The presence of HSV-2 antibodies implies anogenital infection; HSV-1 more difficult to interpret (does not distinguish between oral and genital infection)
6. Consider serology during the following situations:
   • Recurrent or atypical genital symptoms with a negative HCV-1/2 PCR or culture
   • Clinical diagnosis of genital herpes without laboratory confirmation
   • When a patient’s partner has genital herpes
Genital Herpes

Treatment

First Clinical Episode: Acyclovir (400mg orally TID), Famciclovir (250mg orally TID), Valacyclovir (1g orally BID) for 7-10 days

Suppressive Therapy: Acyclovir (400mg orally BID), Valacyclovir (500mg or 1g orally QD), Famciclovir (250mg orally BID), (Reduces frequency by 70-80%)

Prevention:
- Condoms
- Circumcision
- Abstaining from sex when lesion are present
- Asymptomatic transmission possible
- Suppressive therapy (if symptomatic)

Recurrent Episodes: Acyclovir (800mg orally BID for 5 days or TID for 2 days), Valacyclovir (500mg BID for 5 days or 1g QD for 5 days), Famciclovir (1g BID for 1 day, 125mg BID for 5 days, 500mg once followed by 250mg BID for 2 days)
Contact Information

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Director, Center for HIV and STI Prevention, The Miriam Hospital
Chief Medical Officer, Open Door Health
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