Diagnosing and Managing STIs:
An Update from the 2021 CDC STI Treatment Guidelines

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2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Ghanem has no relevant financial relationships with ineligible companies to disclose. (Updated 9/20/21)

Slide 2 of 27

Learning Objectives

After attending this presentation, learners will be able to:

- Describe appropriate diagnostic and management strategies for the most common sexually transmitted infections based on the updated 2021 CDC STI Treatment Guidelines

Slide 3 of 27

Gonorrhea

- The treatment of uncomplicated gonorrhea is now **500 mg of intramuscular ceftriaxone**; if chlamydia is present or is not ruled out, add one week of 100 mg of oral doxycycline taken twice daily
  - Alternate regimens for **urogenital or rectal infections** include oral cefixime 800 mg; intramuscular gentamicin 5mg/kg plus 2 g oral azithromycin
- Patients with pharyngeal gonorrhea should be treated with ceftriaxone- **no alternate regimens are recommended**; a test-of-cure should be performed one to two weeks later
- A reported history of penicillin allergy should prompt clinicians to obtain more information about the nature of that allergy; a majority of these patients may be safely treated with ceftriaxone
- Re-screen all persons diagnosed with gonorrhea in 3 months
- Treat all sex partners in the preceding 60 days of index patients diagnosed with gonorrhea

Disseminated gonococcal infection (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions and usually tender), tenosynovitis, and asymmetrical arthralgia, or (oligoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause **minimal** genital inflammation
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE)
- Differential diagnosis: meningococcemia, RMSF, dengue, endocarditis, Reiter's
- **Test all mucosal surfaces using NAATs and culture (genital, rectal, pharyngeal). Culture is less sensitive but it allows for antimicrobial resistance testing**
- **Treatment: Start with IV ceftriaxone and once clinical status improves, de-escalate to oral regimen based on antimicrobial susceptibility testing. Short courses (i.e. <7 days) are adequate except for meningitis, endocarditis, and septic arthritis.**

What's to be done if a patient reports an allergy to penicillin?

STOP!
DON'T ABANDON CEFTRIAXONE JUST YET
GET MORE INFORMATION ABOUT THE NATURE OF THE PATIENT'S PENICILLIN ALLERGY

The Nature of the Penicillin Allergy

- Is the presentation consistent with drug hypersensitivity?
- If so, is this an immune-mediated reaction?
  - Is it immediate in onset (likely to be IgE-mediated)?
    - Urticarial rash; pruritus; flushing; angioedema of the face, extremities, or laryngeal tissues (leading to throat tightness with stridor, or rarely asphyxiation); wheezing; gastrointestinal symptoms; and/or hypotension
    - Keep in mind: **~80 percent of patients with IgE-mediated penicillin allergy have lost the sensitivity after 10 years**
  - Is it delayed in onset (most often a T-cell-mediated reaction)
    - Contact dermatitis, maculopapular eruptions; SJS; DRESS; drug fevers

The majority (85%+) of persons who report a penicillin allergy can be safely treated with ceftriaxone

Pichler W. UptoDate: Drug hypersensitivity: Classification and clinical features

Chlamydia

- Doxycycline 100mg orally twice daily will be the **preferred option** to treat *Chlamydia trachomatis* infections
  - Azithromycin 1g orally is a second-line regimen
- Azithromycin was 3% less effective when treating urogenital infections compared with doxycycline NEJM 2015; 373;26:2513-2521
- **Two recent RCTs demonstrated that azithromycin was 20% less effective when treating rectal chlamydia infections compared with doxycycline**

Clinical Infectious Diseases
Doxycycline Versus Azithromycin for the Treatment of Rectal Chlamydia in Men Who Have Sex With Men: A Randomized Controlled Trial

- Microbiologic cure was higher with doxycycline than azithromycin (91% [80 of 88] vs 71% [63 of 89]; absolute difference, 20%; 95% CI, 9–31%; P < .001)
- The mechanism of azithromycin treatment failure in rectal CT is not known but is **not** likely due to antibiotic resistance, inadequate tissue penetration of the drug, or the prevalence of LGV biovars.

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*
Andrew Lau, M.S., Fabian Y.S. Kong, Ph.D., Christopher K. Fairley, Ph.D.

- Microbiologic cure occurred in 281 of 290 men (96.9%; 95% CI: 94.9 to 98.9) in the doxycycline group and in 227 of 297 (76.4%; 95% CI, 73.8 to 79.1) in the azithromycin group, for an adjusted risk difference of 19.9 percentage points (95%CI, 14.6 to 25.3; P<0.001)

Testing for Gonorrhea and Chlamydia

Anatomical Site	Specimen type	GC Gram's stain (sensitivity)	GC Culture (Sensitivity)	GC/CT NAATs (Sensitivity)
Male urethra	Swab	Symptomatic: 89-94% Asymptomatic: 40-60%	Symptomatic: 90-95% Asymptomatic: 65-85%	>95% (symptomatic and asymptomatic)
Urine (M/F)	First catch	Not appropriate specimen	Not appropriate specimen	87-95% overall Preferred specimen for men
Endocervical	Swab	37-70% overall (lower for asymptomatic)- specificity is poor	Symptomatic: ~85% Asymptomatic: 65-80%	>95% (symptomatic and asymptomatic)
Vaginal	Swab	Not appropriate specimen	Not appropriate specimen	>95% (symptomatic and asymptomatic) Preferred specimen for women
Throat (M/F)	Swab	Not appropriate specimen	~50%	>95% (symptomatic and asymptomatic)
Rectal (M/F)	Swab	Not appropriate specimen	~50%	>95% (symptomatic and asymptomatic)

Goodhart ME *Sex Transm Dis*. 1982; Schink JC *J Reprod Med*. 1985; Goh BT *Sex Transm Dis* 1985; Tabrizi SN *J Clin Microbiol*. 2011; Doernberg SB *Clin Infect Dis*. 2020

Prevalence of Extragenital Gonorrhea and Chlamydia

Population	NG Prevalence Range (median)	CT Prevalence Range (median)	Comments
Women (33 studies) Rectal Pharyngeal	 0.6 - 35.8% (1.9%) 0 - 29.6% (2.1%)	 2%-77.3% (8.7%) 0.2%-3.2% (1.7%)	Mostly STD clinics; 93% of pharyngeal and 53-100% of rectal NG were asymptomatic. Most women who test positive for rectal infections did NOT report anal sex; extragenital screening increased NG yield by 6-50% compared to genital only testing
MSM (53 studies) Rectal Pharyngeal	 0.2 - 24% (5.9%) 0.5 - 16.5% (4.6%)	 2.1%-23% (8.9%) 0%-3.6% (1.7%)	More extensively studied than in women; 25-100% of extragenital infections were asymptomatic; extragenital screening increased NG yield by 14-85% compared to genital only testing
MSW (9 studies) Rectal Pharyngeal	 0-5.7% (3.4%) 0.4-15.5% (2.2%)	 0%-11.8% (7.7%) 0%-22% (1.6%)	Some participants may have engaged in same sex behaviors (sexual identity vs. sexual behaviors)
Screen all sexually active MSM at all sites of exposure; consider screening women at all sites of exposure after discussing with patient			

Chan PA *Infect Dis Obstet Gynecol* 2016

Proctitis

	Proctitis	Proctocolitis
Symptoms	Anorectal pain, tenesmus, rectal discharge	Proctitis symptoms, may also have diarrhea, abdominal cramps, inflammation of colonic mucosa extending to 12 cm above the anus
Etiologic organisms	Gonorrhea, Chlamydia (including LGV), Syphilis, Herpes	LGV, (also Campylobacter, Shigella, Entamoeba histolytica, CMV)
Initial testing	In both: NAAT for GC/CT, Syphilis serologies, HSV (PCR) *note: Syphilis and LGV can mimic IBD.	

Lymphogranuloma Venereum (LGV)

- **L1-L3 serovars** of *Chlamydia trachomatis*: **LGV**
  - Rectal CT NAAT will be positive
  - Clusters reported in Europe, US (especially in HIV+ MSM)
- Clinical:
  - Primary lesion: non painful ulcer 3-21 days
  - Secondary lesions 10 days to 6 months
    - Tender inguinal/femoral adenopathy (buboes)
    - Systemic symptoms
    - <u>Proctitis, Proctocolitis</u>

Cluster of Lymphogranuloma Venereum Cases Among Men Who Have Sex with Men — Michigan, August 2015–April 2016

Alex de Voux, PhD[1,2]; James B. Kent, MS[3]; Kathryn Macomber, MPH[3]; Karen Krzanowski, MA, MPH[4]; Dawn Jackson[4]; Tayneata Starr[4]; Sandra Johnson[4]; Deborah Richmond, MSN[5]; Lawrence R. Crane, MD[5]; Jonathan Cohn, MD[5]; Christopher Finch[5]; Jevon McFadden, MD[6]; Allan Pillay, PhD[2]; Cheng Chen, PhD[2]; Laurie Anderson[2]; Ellen N. Kersh, PhD[2]

Chlamydia Proctitis

MMWR

Sexually Transmitted Infections Treatment Guidelines, 2021

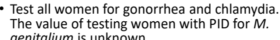
- There are currently no <u>commercial</u> tests that distinguish between LGV and non-LGV strains of *Chlamydia trachomatis*
- The treatment duration for chlamydia **<u>proctitis</u>** depends on symptoms:
  - **Asymptomatic and mildly symptomatic** persons should be treated with **<u>one week</u>** of doxycycline
  - **Moderately to severely symptomatic persons** should be treated with **<u>3 weeks</u>** of doxycycline

PID

MMWR

Sexually Transmitted Infections Treatment Guidelines, 2021

- Test all women for gonorrhea and chlamydia. The value of testing women with PID for *M. genitalium* is unknown
- The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion. If an IUD user receives a diagnosis of PID, the IUD does not need to be removed
- Until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, **using regimens with anaerobic activity should be considered**



All outpatient regimens to treat PID are cephalosporin-based

Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease
Ceftriaxone 500 mg IM in a single dose*
PLUS
Doxycycline 100 mg orally 2 times/day for 14 days
WITH
Metronidazole 500 mg orally 2 times/day for 14 days
OR
Cefoxitin 2 gm IM in a single dose and Probenecid 1 gm orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally 2 times/day for 14 days
WITH
Metronidazole 500 mg orally 2 times/day for 14 days
OR
Other parenteral third generation **cephalosporin** (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally 2 times/day for 14 days
WITH
Metronidazole 500 mg orally 2 times/day for 14 days
*For persons weighing ≥150 kg (~300 lbs.) with documented gonococcal infection, 1 gm of ceftriaxone should be administered.

Managing Urethritis

- If a patient presents with urethritis, test for both GC and CT and treat for both empirically with ceftriaxone and doxycycline [if you are able to do a Gram's stain, or have access to another POC diagnostic, and it does not show evidence of GC, just treat for CT with doxycycline]
- If the patient has persistent symptoms and there are **objective signs** for urethritis (≥2 WBCs/HPF in high-prevalence settings [STI clinics] or ≥5 WBCs/HPF in lower-prevalence settings OR positive leukocyte esterase test on first-void urine OR microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBCs/HPF):
  - Test MSW for both trichomonas and *M genitalium*
  - Test MSM for *M genitalium*
- Treat the patients with persistent symptoms based on testing results

Mycoplasma genitalium: Testing and Treatment

- NAATs now FDA-cleared
- Test men with persistent urethritis and women with persistent cervicitis
- CONSIDER testing women with PID
- Do NOT routinely test extragenital sites
- Do NOT screen asymptomatic men or women
- Partners: If you can test partners, treat those who are positive; if you cannot, consider treating the partner with the same regimen used to treat the patient

Two-stage therapy approaches, (ideally using resistance-guided therapy) are recommended for treatment:

Recommended Regimens if *M. genitalium* Resistance Testing Is Available
If macrolide sensitive: Doxycycline 100 mg orally 2 times/day for 7 days, followed by **azithromycin** 1 g orally initial dose, followed by 500 mg orally daily for 3 additional days (2.5 g total)
If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days followed by **moxifloxacin** 400 mg orally once daily for 7 days

Recommended Regimen if *M. genitalium* Resistance Testing Is Not Available
If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by **moxifloxacin** 400 mg orally once daily for 7 days

Syphilis Serologies

- **Nontreponemal (lipoidal) tests: RPR and VDRL**
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (older age; autoimmune diseases; HIV & other infections)
  - **May become nonreactive over time with or without treatment**
- **Treponemal tests: (EIA, CIA, FTA-ABS, TPPA, etc.)**
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (non-syphilitic treponematoses; severe gingivitis)
  - **Once reactive always reactive-independent of treatment history**

Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*

Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

* The traditional algorithm starts with a nontreponemal test (NTT) followed, if reactive, by a confirmatory treponemal test (TT). The reverse-sequence algorithm starts with a TT (e.g., fluorescent treponemal-antibody absorption test, Treponema pallidum particle agglutination test, or automated enzyme or chemiluminescence immunoassay), followed, if reactive, by an NTT. RPR denotes rapid plasma reagin, and VDRL Venereal Disease Reference Laboratory.
† The confirmatory TT should be different from the TT performed initially.
‡ The likely or most likely interpretation of test results is noted for each algorithm.
§ Causes of a biologic false positive NTT include older age, autoimmune diseases, infections (e.g., human immunodeficiency virus infection), and drug use; pregnancy as a cause is controversial.
¶ Causes of a biologic false positive TT include infections (e.g., Lyme disease), autoimmune diseases, and older age.

Ghanem NEJM 2020

What to do with RPR Titers that Don't Respond Appropriately

- **Lack of a fourfold decline in titers** after waiting a **full 12m** following therapy for early syphilis and a **full 24m** following therapy for late syphilis:
  - Any neurological signs/symptoms? **If yes, perform immediate LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If both of the above are negative, you can either follow the patient carefully or you can give additional antibiotics. Several observational studies suggest that there are **NO short/intermediate-term benefits to additional antibiotics**
- A **four-fold increase in titers** after appropriate therapy:
  - Any neurological signs/symptoms? **If yes, perform immediate LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If the patient denies the possibility of reinfection, and the titer continues to be elevated when repeated two weeks later, **consider performing a LP**

Syphilis: CSF Examination

- Perform a lumbar puncture (LP) in persons who:
  - Have neurological signs and symptoms
  - Are diagnosed with tertiary syphilis (cardiovascular, gummas)
  - Consider in those who are asymptomatic but whose serological titers increase four-fold after stage-appropriate therapy and in whom the likelihood of reinfection is low
- No data to support routine LP in asymptomatic HIV-infected persons
- No need for follow-up LP 6 months after the diagnosis and treatment of neurosyphilis in HIV uninfected or PLWH who are on ART if they improve clinically, and their serological titers are responding appropriately

Otic and Ocular Syphilis Take-Home Points

Otosyphilis

- **Clinical manifestations**: cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Symptoms: **Hearing loss, vertigo, and/or tinnitus** (ringing in the ears)
  - Diagnosis is presumptive; **CSF examination is normal in 90% of cases and is NOT recommended if patient only has otic signs and symptoms**
- **Therapy**: IV penicillin (+ corticosteroids)
- **Prognosis**: 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo

Ocular Syphilis

- Clinical manifestations: any portion of the eye; any ocular manifestation; **immediate ophthalmological examination**
  - Symptoms: Redness, pain, floaters, flashing lights, visual acuity loss
  - Diagnosis is presumptive; **CSF examination is normal in 40% of cases and is NOT recommended if patient only has ocular signs and symptoms**
- **Therapy**: IV penicillin (+ corticosteroids)

Syphilis During Pregnancy

- Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroin use, incarceration of the woman or her partner, and unstable housing or homelessness
- Certain evidence indicates that additional therapy is beneficial for pregnant women to prevent congenital syphilis. **For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose**
- Missed doses **>9 days** between doses are not acceptable for pregnant women receiving therapy for late latent syphilis

HSV-2 Serological Diagnosis: 2-Step Testing

- If lesions are presents, PCR is the best diagnostic test
- If lesions are absent, the recommended serological tests for HSV-1 and HSV-2 are the Glycoprotein-G-based IgG EIAs [e.g., HerpeSelect HSV EIA]
  - There are issues with the SPECIFICITY of the IgG-2 EIAs with EIA index values <3.0 [in one study, the specificity was 38%]
  - Laboratories should provide index values for all HSV-2 IgG EIA results
  - **If the index value <3.0, a second more specific test should be performed to confirm the original EIA result**. There are two options for the second test:
    - HSV-2 Western Blot- only performed at the University of Washington
      - https://depts.washington.edu/uwviro/
    - HSV-2 *Biokit Rapid Test* (Biokit USA, Lexington MA)
- **NEVER IgM serologies**- they are neither sensitive nor specific to diagnose a recent infection

Agyemang *STD* 2017

HSV: HIV & Pregnancy

- In PWH with a CD4 < 200 cells/mm^3 and a history of genital herpes, consider 6 months of HSV suppressive therapy when initiating ART to decrease reactivation of genital herpes
- During pregnancy: At the onset of labor, all women should be questioned thoroughly about symptoms of genital herpes, including prodromal symptoms (e.g., pain or burning at site before appearance of lesion), and all women should be examined thoroughly for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally.

Trichomonas vaginalis

- Majority of infections asymptomatic in both men and women; causes vaginitis and NGU (especially among heterosexual men)
- Older women and MSW are at higher risk
- Diagnosis: culture and **PCR**; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: **Metronidazole 500mg PO BID X 7 days for all women** [never use topical gel formulations]; Metronidazole 2g PO X1 is ok for men; **Tinidazole 2g orally X1 ok for both men and women**
  - Recent study suggests that 1 week of metronidazole better than 2g in HIV-uninfected women (Kissinger P, et al. *Lancet Infectious Diseases* 2018)
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance
- Partners in the preceding 60 days must be treated
- **Screen HIV+ women annually**

Thank you!

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Question-and-Answer Session

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