2021 STI Treatment Guidelines

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Clinical Associate Professor, University of WA
August 25, 2021
Disclosure

• Hillary Liss has no relevant financial relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on patients.
Syphilis management? Resistant gonorrhea? STD treatment?

GOT A TOUGH STD QUESTION?
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Ask your question  National STD experts review  Response within 1-5 business days, depending on urgency

Log on to www.STDCCN.org for medical professionals nationwide

A product of the National Network of STD Clinical Prevention Training Centers www.NNPTC.org
2019 was worst year on record for reported STIs

THE STATE OF STDs IN THE UNITED STATES, 2019

STDs increased for the 6th year, reaching a new all-time high

- 1.8 million cases of Chlamydia, 19% increase since 2015
- 616,392 cases of Gonorrhea, 56% increase since 2015
- 129,813 cases of Syphilis, 74% increase since 2015
- 1,870 cases of Syphilis among newborns, 279% increase since 2015

OVER HALF OCCURRED AMONG YOUNG PEOPLE 15-24 years of age

New guidelines

• Hot off the presses!
• July 23, 2021

US Public Health Service
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES-2021 UPDATE
A Clinical Practice Guideline

• Expected later in 2021
What’s in a name?

**STD**
- Sexually transmitted disease
- Refers to disease state

**STI**
- Sexually transmitted infection
- Refers to pathogen
- Often asymptomatic
Evidence-based Approach to Guideline Development

CDC Staff + Subject Matter Expert → Systematic Review of Evidence

Key Question Development

Guidelines 3-day Meeting June 2019

Answer the “Key Questions”

Quality of the evidence (USPSTF)

Identify critical gaps in knowledge (research agenda)

Tables of evidence

Background papers

2021 Guidelines

Evidence-based Approach to Guideline Development

- Systematic Review of Evidence
- Key Question Development
- Guidelines 3-day Meeting June 2019
- Answer the “Key Questions”
- Quality of the evidence (USPSTF)
- Identify critical gaps in knowledge (research agenda)
- Tables of evidence
- Background papers
- 2021 Guidelines
CDC STI Treatment Guideline Development

- Evidence-based on principal outcomes of STI therapy
- “Recommended” regimens preferred over “alternative” regimens
- Treatments alphabetized unless there is a priority of choice
- Released July 2021
  - Available at: https://www.cdc.gov/std/treatment-guidelines/toc.htm
  - Interim app download: https://www.cdc.gov/STIapp/
Screening
# STI Screening for Cis-Women (WSM and WSW)

<table>
<thead>
<tr>
<th>Women under 25 years of age</th>
<th>Chlamydia/gonorrhea</th>
<th>HIV at least once</th>
<th>Hep C at least once if ≥ 18 yo (unless prevalence of Hep C &lt; 0.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women 25 years of age and older</td>
<td>Chlamydia/gonorrhea if at risk</td>
<td>HIV at least once</td>
<td>Hep C at least once (unless prevalence of Hep C &lt; 0.1%)</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Chlamydia (&lt;25 years of age or risk and retest during 3rd trimester)</td>
<td>Gonorrhea (&lt;25 years of age or risk and retest during 3rd trimester)</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Syphilis serology</td>
<td>HepB sAg</td>
<td>Hep C (unless prevalence of Hep C &lt; 0.1%) WITH EVERY PREGNANCY</td>
</tr>
</tbody>
</table>

Screening not recommended for M. genitalium or trichomonas
STI Screening for Transgender Persons

Based on current anatomy and gender of sex partners

• Offer HIV screening to all transgender persons
• TG persons who have sex with cisgender men, at similar risk for STIs as cis-MSM

Transgender women post vaginoplasty

• GC/CT (all sites of exposure: oral, anal, genital)
(Urine vs neovaginal swab not specified, best specimen type based on tissue type used to construct neovagina)

Transgender Men post metoidioplasty

• If vagina still present and need to screen for STIs, cervical (or vaginal) swab should be used
### STI Screening for cis-MSM

- HIV*
- Syphilis*
- Urethral GC and CT*
- Rectal GC and CT (if receptive anal sex)*
- Pharyngeal GC (if oral sex)*
- Hepatitis B (HBsAg, HBV core ab, HBV surface ab)
- **Hepatitis C:** (At least once if ≥ 18 yo, unless prevalence of infection < 0.1%)
- Anal cancer: annual digital anorectal exam may be useful (no anal Pap rec yet)
- HSV-2 serology (consider)

- At least annually, more frequent (3-6 months) if multiple/anonymous partners, drug use, or partners w/ risk
- Routine screening not recommended for M. genitalium
What about “Extragenital” Screening?

- Extragenital screening = testing for STIs at any body site other than genitourinary (urethral/urine/vaginal/cervix)
- Usually refers to rectal and oropharynx
- Typically for gonorrhea and/or chlamydia only
- Recommended routinely only for men who have sex with men (MSM), but now permissive for other individuals
Importance of Extragenital GC/CT Infections

- Transmission
  - 30% of symptomatic gonococcal urethritis is attributable to oro-pharyngeal exposure\(^1\)
- HIV Transmission
  - Can potentiate acquisition, even after controlling for sexual behaviors\(^2\)\(^-\)\(^4\)
- Treatment can differ
  - Pharyngeal GC\(^5\)
    - Ceftriaxone > Cefixime
  - Rectal CT\(^6\)
    - Doxy >>> Azithromycin

Extragenital Gonorrhea & Chlamydia is Common

- Among MSM, high rates of extra-genital GC & CT
  - Pharyngeal GC: 9.2%\textsuperscript{1}
  - Rectal GC: 9.7%\textsuperscript{3}
  - Rectal CT: 12%\textsuperscript{3}

- The majority of infections are asymptomatic
  - 92% of pharyngeal GC\textsuperscript{2}
  - 84 - 86% of rectal GC\textsuperscript{2}

\textsuperscript{1} Kent CK. CID 2005
\textsuperscript{2} Morris, CID 2006
\textsuperscript{3} Barbee, STD 2014
Don’t forget the triple dip: STD Screening for MSM

Annually for all sexually active MSM
Every 3-6 months for high-risk MSM

- Syphilis & HIV serology
- Pharyngeal GC
- Urine GC/CT
- Rectal GC/CT
STI Self-Testing Program

Available in English and Spanish

Email aradford@uw.edu or go to https://www.uwptc.org/visual-guides for free posters for your clinic
STI Screening for cis-MSW

- Routine STI screening not recommended
  - GC/CT recommended in high prevalence settings (e.g. adolescent clinics, correctional facilities, and STI clinics)
- HIV at least once (between 13-64 years of age)
- Hep C at least once if ≥ 18 yo (unless prevalence of Hep C < 0.1%)
<table>
<thead>
<tr>
<th>Category</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>• &lt; 25 annually, 25+ if at risk</td>
</tr>
<tr>
<td></td>
<td>• Pregnant &lt;25 or risk</td>
</tr>
<tr>
<td>MSM</td>
<td>• 3-6 month intervals at all exposed sites: genital, rectal, pharyngeal</td>
</tr>
<tr>
<td>MSW</td>
<td>• High prevalence settings (e.g., Corrections, STI Clinics, adolescents)</td>
</tr>
<tr>
<td>Persons living with HIV</td>
<td>• At least annually</td>
</tr>
<tr>
<td></td>
<td>• All exposed sites: genital, rectal, pharyngeal</td>
</tr>
<tr>
<td>Patients on PrEP</td>
<td>• Every 3-6 months</td>
</tr>
<tr>
<td></td>
<td>• All exposed sites</td>
</tr>
<tr>
<td>Adolescents</td>
<td>• Consider rectal/pharyngeal screen based on reported behavior/exposure</td>
</tr>
<tr>
<td>Category</td>
<td>Screening Recommendations</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Pregnancy                 | • At first prenatal visit  
• Again at 28 weeks and at delivery (if at high risk, or residing in area with high syphilis morbidity) |
| MSM                       | • Including those on PrEP, 3-6 month intervals                                           |
| Corrections               | • Universal opt out screening on intake based on local area or institutional incidence   |
| Persons living with HIV   | • At least annually                                                                     |
| STI Clinic patients       | • Regardless of symptoms  
• If other STI diagnosed                                                                 |
Who should be screened for HIV?

- CDC recommends: At least one time screening for all patients aged 13-64 years
  - All persons who seek STI screening
- USPSTF recommends:
  - Screen people aged 15 to 65 years
  - Risk-based screening for younger adolescents & older adults
  - Pregnant women regardless of age
Chlamydia
Doxycycline vs Azithromycin for Urogenital Chlamydia

Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Doxycycline</th>
<th>Azithromycin</th>
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</thead>
<tbody>
<tr>
<td>Kong</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>Khos '14</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>Kissinger</td>
<td>89%</td>
<td>93%</td>
</tr>
<tr>
<td>Khos '18</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>D-Muijrs</td>
<td>95% 94%</td>
<td>100%</td>
</tr>
<tr>
<td>Geisler</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Beyda</td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>

Slide credit: Dr. Will Geisler
Doxycycline vs Azithromycin for Rectal Chlamydia

Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Doxycycline</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kong '15</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>D-Muijers</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Gratrix</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Hathorn</td>
<td>99%</td>
<td>94%</td>
</tr>
<tr>
<td>Li</td>
<td>94%</td>
<td>81%</td>
</tr>
<tr>
<td>Kong '16</td>
<td>84%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Slide credit: Dr. Will Geisler
Randomized Controlled Trial DOX vs AZM for Rectal CT: Microbiologic Cure at 4 Weeks

Dombrowski J, 2021, CID https://doi.org/10.1093/cid/ciab153
Chlamydia Treatment: Urogenital/ Rectal/ Pharyngeal

Recommended regimens (non-pregnant):

- Doxycycline 100 mg orally twice daily for 7 days*

Alternative regimens (non-pregnant):

- Azithromycin 1 g orally in a single dose OR
- Levofloxacin 500 mg orally once daily for 7 days

*Doxycycline delayed-release 200 mg, once-daily dosing for 7 days effective for urogenital CT. More costly but lower frequency GI side effects than standard doxycycline.
Chlamydia Treatment: Pregnancy

**Recommended regimen (pregnant*):**

- Azithromycin 1 g orally in a single dose

**Alternative regimens (pregnant*):**

- Amoxicillin 500 mg orally three times a day for 7 days

* Test of cure at 3-4 weeks only in pregnancy
Expedited Partner Therapy for GC/CT

- No states in US prohibit EPT (either allowable or potentially allowable by law/statute in all 50 states)
- Previously only recommended for hetero men/women, now “shared decision making” for EPT for MSM
- Providing patients with packaged oral medications is preferred approach
  - Partners (especially adolescents) may not fill prescriptions
Sure feels like there are a lot of changes for me in the 2021 CDC STI Guidelines!

Hold my beer...
Gonorrhea
More than half of GC isolates are resistant to at least one antibiotic

Prevalence of Resistant or Decreased Susceptibility of *N. gonorrhoeae* Isolates to Antimicrobials, GISP, 2009 and 2019*

*2019 data are preliminary*
New* Gonorrhea Treatment Guidelines
for uncomplicated infections

Ceftriaxone 500 mg IM x 1
for persons weighing <150kg*

*For persons weighing ≥ 150 kg, 1 g of IM ceftriaxone should be administered

No longer recommending dual therapy with azithromycin

Test-of-Cure at 7-14 days post treatment for pharyngeal gonorrhea

Doxycycline 100 mg PO BID x 7 days

However, if chlamydia has not been excluded, treat for chlamydia with:

For pregnancy, allergy, or concern for non-adherence, 1 g PO azithromycin x 1 can be used

Update to CDC's Treatment Guidelines for Gonococcal infection, 2020; MMWR
*New* **Alternative** Gonorrhea Treatment

for uncomplicated infections of the cervix, urethra, and rectum **if ceftriaxone is not available**:

- **Cefixime 800 mg PO x 1**
- **Doxycycline 100 mg PO BID x 7 days**

However, if chlamydia has not been excluded, treat for chlamydia with:

- **Gentamicin 240 mg IM + azithromycin 2 g PO**

For pregnancy, allergy, or concern for non-adherence, 1 g PO azithromycin x 1 can be used.

No reliable alternative treatments are available for **pharyngeal** gonorrhea.

Update to CDC's Treatment Guidelines for Gonococcal infection, 2020; MMWR
Rationale for GC Treatment Changes

- Improved antimicrobial stewardship
- Pharmacokinetic and pharmacodynamic considerations
- Changes in azithromycin susceptibility in GC
Antimicrobial Stewardship

Need to minimize antibiotic exposure unless benefit outweighs risk

Risk benefit of dual vs monotherapy for GC

Drug-Resistant GC Urgent Threat

- Azithromycin resistance is a concern for other bacteria, so want to reduce overall use of azithromycin
Pharmacodynamics/ Pharmacokinetics

- Antibiotic most effective when drug levels are above MIC (minimum inhibitory concentration): lowest concentration of antibiotic needed to kill the bacteria
- Ceftriaxone kills GC when levels are high enough for long enough
  - 20-24 hours for Ceftriaxone
  - 500 mg dose most effective
  - Via modeling/mouse model
- Higher dose also more likely to kill gonorrhea in the pharynx
Rise in GC Isolates with Decreased Susceptibility to Azithromycin (~5%) Gonococcal Isolate Surveillance Project (GISP), 2010–2019

NOTE: Elevated MIC = Azithromycin: ≥ 2.0 µg/mL; Cefixime: ≥ 0.25 µg/mL; Ceftriaxone: ≥ 0.125 µg/mL
Mycoplasma genitalium
More than 1 in 4 men with urethritis have *Mycoplasma genitalium*

**MAGNUM STUDY**

Men with urethritis symptoms were enrolled from 6 U.S. STD clinics during 6/2017–8/2018

<table>
<thead>
<tr>
<th>Study Site (n)</th>
<th>Prevalence of MG (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durham, NC (n=93)</td>
<td>24.7 (16.0–33.5)</td>
</tr>
<tr>
<td>Greensboro, NC (n=152)</td>
<td>38.8 (31.1–46.6)</td>
</tr>
<tr>
<td>Pittsburgh, PA (n=174)</td>
<td>27.6 (20.9–34.2)</td>
</tr>
<tr>
<td>Birmingham, AL (n=235)</td>
<td>29.8 (23.9–35.6)</td>
</tr>
<tr>
<td>New Orleans, LA (n=103)</td>
<td>29.1 (20.4–37.9)</td>
</tr>
<tr>
<td>Seattle, WA (n=157)</td>
<td>20.4 (14.1–26.7)</td>
</tr>
<tr>
<td><strong>TOTAL (n=914)</strong></td>
<td><strong>28.7 (23.8–33.6)</strong></td>
</tr>
</tbody>
</table>
M. genitalium screening and diagnostic testing

- Population based screening for M. genitalium is not recommended

- Diagnostic testing: NAAT (FDA approved in 2019) for urine, urethral, penile meatal, endocervical, vaginal specimens

- When to test: persistent urethritis that fails initial treatment, also consider for persistent PID or cervicitis
Over 50-60% of M. genitalium infections have resistance mutations to macrolides (azithro)

National Institutes of Health [HHSN2722013000121, HHSN272000010, DIMD16-0039]

Bachmann LH, Kirkcaldy RD, et al. CID 2020

Slide credit: L Bachmann
Resistance guided therapy: *M. genitalium*

Empiric Therapy for urethritis, cervicitis, PID, proctitis and/or self-reported sexual contact to MG+ partner

- **Doxycycline**
  - (100mg bid x 7d)
  - N=383

Macrolide sensitive (N=109)
- AZM 1g followed by 500mg x 3d (2.5g total)
- 95.4%
  - (95% CI 89.7-98.0)

Macrolide resistant (N=274)
- MOXI 400mg qd x 7d
- 92.0%
  - (95% CI 88.1-94.6)

Selected macrolide resistance in ≤3.8%*

*Durukan and Read studies combined


Slide credit: L Bachmann
M. genitalium Treatment

Sequential treatment for suspected/documentated M. genitalium

Start with Doxycycline to reduce bacterial load

- **Doxycycline 100 mg BID x 7 days**

  **THEN**
  
  **Moxifloxacin 400 mg BID x 7 days**

If local macrolide resistance is low or known macrolide sensitive

- **Doxycycline 100 mg BID x 7 days**

  **THEN**
  
  **Azithromycin 2.5 gm over 4 days**

(Azithromycin- 1 gm x 1 day then 500 mg x 3 day)

Trichomonas
T. Vaginalis screening and diagnostic testing

• Screening for T. vaginalis is recommended for
  • Cis-women with HIV
  • Cis-women in correctional settings
  • Consider for other high prevalence settings
• Diagnostic testing: NAAT for urine, urethral, endocervical (including liquid cytology), vaginal
  • When to test: symptomatic patients
Treatment Consideration:
Single dose metronidazole is not as effective as 7 days

- Single dose previously recommended for trich in HIV-negative women, 7-day therapy (500 mg BID) recommended for patients with HIV (CDC TX GL 2015)
- N=623 women randomized 1:1 to single dose MTZ vs 7 day
- Culture TOC, 6-12 days post treatment

![Cured at Follow-up](chart.png)

Kissinger, 2018 Lancet Infect Dis Dis
# Trichomoniasis Treatment

**Recommended regimen:** **Vaginal trichomonas (HIV+/HIV-)**

- **Metronidazole 500 mg PO BID x 7d**

- **Metronidazole 2 g PO single dose for men w/ trichomonas or male partners**

**ACOG 2020 Treatment Guidelines**

- Metronidazole 500 mg PO BID x 7 d

**Change in 2021 STI Treatment Guidelines**

Metronidazole and Alcohol

- Metronidazole does not actually inhibit acetaldehyde dehydrogenase (as occurs with disulfiram)
- Evidence review: no in vitro or clinical studies, no animal models, and no adverse event reporting
- Refraining from ETOH is unnecessary during treatment

Change in 2021 STI Treatment Guidelines

2021 CDC STI Treatment Guidelines

Fjeld H, Raknes G. Tidsskr Nor Laegeforen. 2014;134(17):1661–3
Test of Cure vs Retesting
## Test of Cure vs Retesting

<table>
<thead>
<tr>
<th>TEST OF CURE</th>
<th>Time period</th>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC (pharynx)</td>
<td>2 weeks</td>
<td>All patients</td>
</tr>
<tr>
<td>CT (cervix)</td>
<td>4 weeks</td>
<td>Pregnant patients only</td>
</tr>
<tr>
<td>LGV (all sites)</td>
<td>4 weeks</td>
<td>If AZM used instead of DOX (consider)</td>
</tr>
<tr>
<td>M. genitalium</td>
<td>3 weeks</td>
<td>If DOX + AZM used instead of MOXI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RETEST FOR REINFECTION</th>
<th>Time period</th>
<th>Who</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC/CT/LGV (all sites)</td>
<td>3 m (anytime from 1-12 m ok)</td>
<td>All patients</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>3 m (anytime from 1-12 m ok)</td>
<td>Patients w/vaginal infection</td>
</tr>
</tbody>
</table>
Syphilis
Syphilis Diagnosis and Treatment

• Neurosyphilis Dx in pts with reactive serology and...
  • Ocular symptoms: if isolated ocular sx, no CN or other neuro involvement, and confirmed eye abnormalities on exam, no CSF exam needed before tx
  • Otosyphilis: if isolated auditory abnormalities, CSF likely to be normal, no CSF needed before tx
• Follow up: if RPR drops appropriately and patient improves clinically, no repeat CSF needed for pts without HIV or patients with HIV on ART
• Treatment: no changes for any stage of syphilis
Pelvic Inflammatory Disease
PID Outpatient Treatment: Should Metronidazole be used routinely?

- Randomized Controlled Trial (N=233 cis women)
- Ceftriaxone 250 mg IM **plus** Doxycycline 100 mg PO BID x 14 days **plus**
  - Metronidazole 500 mg BID x 14 day  **OR**
  - Placebo BID X 14 day
- Primary outcome: Clinical improvement 3 days
- Additional outcomes: Anaerobic organisms in endometrium at 30 days, fever, CMT reduction
Study Results

- Clinical improvement at 3 days similar between two arms
- Metronidazole
  - Reduced anaerobes in endometrium (8% vs 21%, p<0.05)
  - Reduced M. genitalium (cervical) (4% vs 14%, p<0.05)
  - Reduced CMT/pelvic tenderness (9% vs 20%, p<0.05)

Conclusion: **Metronidazole should be routinely added for PID RX**

Wisenfeld et al. CID 2021
PID IM/Oral Treatment Regimens: Metronidazole for all

Oral regimens:

- Ceftriaxone 500 mg IM (or other parenteral 3rd generation cephalosporin) x 1 or
- Cefoxitin 2 g IM with probenecid 1 g orally once
  PLUS
- Doxycycline 100 mg orally twice daily for 14 days
  WITH OR WITHOUT
- Metronidazole 500 mg orally twice daily for 14 days
Acknowledgments

- Ina Park- UCSF, California Prevention Training Center
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- Sancta St. Cyr- CDC
- Will Geisler- University of Alabama Birmingham
- Sharon Adler- UCSF, California Prevention Training Center
- Chris Fox- OHSU
GOT A TOUGHC STD QUESTION?
Get FREE expert STD clinical consultation at your fingertips

Ask your question
National STD experts review
Response within 1-5 business days, depending on urgency

Log on to www.STDCCN.org for medical professionals nationwide
Thank you!!

Any Burning Questions?

Hillary Liss
hliss@uw.edu
206-399-4590
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