Gonorrhea and Chlamydia Infections: 2019 Update on Testing, Treatment, and Antibiotic Resistance

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Faculty, California Prevention Training Center

ROADMAP

- Surveillance
- Clinical syndromes
- Screening recommendations
- Diagnostics
- Treatment updates
- Antibiotic-resistant gonorrhea
- Partner treatment
- Retesting
STDs IN THE UNITED STATES

- CHLAMYDIA: 1,708,569 total cases in 2017, 6.89% increase since 2016
- GONORRHEA: 555,608 total cases in 2017, 18.58% increase since 2016
- SYPHILIS: 30,644 total cases in 2017, 10.17% increase since 2016
- CONGENITAL SYPHILIS: 918 total cases in 2017, 43.66% increase since 2016

STDs tighten their grip on the nation's health as rates increase for a fourth year.

Source: U.S. Centers for Disease Control and Prevention

The STATE of STDs in the United States in 2017

- 1.7 million cases of chlamydia, 22% increase since 2013
- 555,608 cases of gonorrhea, 67% increase since 2013
- 30,644 cases of syphilis, 76% increase since 2013

SHARP INCREASES in syphilis among newborns in the US continue, improved testing and treatment needed for pregnant women.

CLINICAL SYNDROMES

CERVICITIS, URETHRITIS

STD Atlas, 1997
NORMAL TUBES/OVARIES and PELVIC INFLAMMATORY DISEASE

Source www.dallasivf.com

PHARYNGITIS, EPIDIDYMITIS, and PROCTITIS

STD Atlas, 1997
CONJUNCTIVITIS

DISSEMINATED GONOCOCCAL INFECTION

STD Atlas, 1997
**REACTIVE ARTHRITIS**

**CONJUNCTIVITIS, OLIGOARTHRITIS, CIRCINATE BALANITIS**

*DOIA Website, 2000*

*STD Atlas, 1997*

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**NEONATAL CONJUNCTIVITIS and PNEUMONITIS**

*STD Atlas, 1997*
SCREENING/DIAGNOSTICS

WHICH PATIENT DOES NOT NEED TESTING FOR CT/GC?

a) Amanda, a cisgender woman with male and female sex partners. She was treated for CT 3 months ago. She was negative for GC and HIV. No new partners, no symptoms.

a) Jeff, a cisgender MSM, who had receptive and insertive anal sex with 10 partners in the last year. He had a negative urine, throat, and rectal screen for CT, GC, syphilis, and HIV 3 months ago.

a) Dave, a cisgender man with exclusively female partners. He screened negative for CT, GC, and HIV 6 months ago. He has had no new partners, no symptoms.

a) Martha, a transgender woman with male partners. She is on PrEP for HIV prevention and screened negative for CT, GC, syphilis, and HIV 3 months ago. She has had no new partners and no symptoms.
### WHICH PATIENT DOES **NOT** NEED TESTING FOR CT/GC?

- **a)** Amanda, a cisgender woman with male and female sex partners. She was treated for CT 3 months ago. She was negative for GC and HIV. No new partners, no symptoms.

- **a)** Jeff, a cisgender MSM, who had receptive and insertive anal sex with 10 partners in the last year. He had a negative urine, throat, and rectal screen for CT, GC, syphilis, and HIV 3 months ago.

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- **a)** Martha, a transgender woman with male partners. She is on PrEP for HIV prevention and screened negative for CT, GC, syphilis, and HIV 3 months ago. She has had no new partners and no symptoms.

### WHO SHOULD BE SCREENED FOR CT/GC?

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>• &lt; 25 annually, 25+ if at risk&lt;br&gt;• Pregnant (first trimester)</td>
</tr>
<tr>
<td><strong>MSM</strong></td>
<td>• At least annually&lt;br&gt;• Exposed sites: genital, rectal, throat</td>
</tr>
<tr>
<td><strong>Hetero Cis Men</strong></td>
<td>• High prevalence settings (corrections, STD clinics)</td>
</tr>
<tr>
<td><strong>HIV +</strong></td>
<td>• At least annually&lt;br&gt;• All exposed sites</td>
</tr>
<tr>
<td><strong>Patients on PrEP</strong></td>
<td>• Every 3 months</td>
</tr>
<tr>
<td><strong>Post-Tx</strong></td>
<td>• All patients, 3 months after treatment</td>
</tr>
</tbody>
</table>

CDC 2015 STD Tx Guidelines [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)

Plus: Guidelines for HIV care and PrEP

**CT / GC NAAT: EXTRAGENITAL (RECTAL & PHARYNGEAL) TESTS**

*FDA NEWS RELEASE*

FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea

Today, the U.S. Food and Drug Administration cleared for marketing two tests that can detect the presence of the bacteria Chlamydia trachomatis and Neisseria gonorrhoeae, which cause the sexually-transmitted infections, respectively, chlamydia and gonorrhea, through diagnostic testing of extragenital specimens. The Aptima Combo 2 Assay and the Xpert CT/NG are the first devices cleared for extragenital diagnostic testing of these infections via the throat and rectum. These tests were previously only cleared for testing urine, vaginal and endocervical samples.

For more information:


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**LAB ORDERING & BILLING CODES**

<table>
<thead>
<tr>
<th>Company-Specific Ordering Codes for Combined GC/CT Nucleic Acid Amplified Tests (NAATs)</th>
<th>Company-Specific Ordering Codes for CT test only</th>
</tr>
</thead>
<tbody>
<tr>
<td>LabCorp*</td>
<td>Quest*</td>
</tr>
<tr>
<td>Rectal</td>
<td>188672</td>
</tr>
<tr>
<td>Pharyngeal</td>
<td>188698</td>
</tr>
</tbody>
</table>

NAATs are offered at (or from) any location in the country with these two codes.

For information on specimen collection and transportation, clinicians should contact the local reference laboratory representative.

**CPT Billing Codes**

- CT detection by NAAT 87491
- GC detection by NAAT 87591

- CDC does not endorse these laboratories, however, they represent the largest laboratories nationally. There may be other private laboratories that have verified rectal and pharyngeal testing with NAATs. Many PHLs have also verified rectal and pharyngeal testing.
SUBOPTIMAL STD SCREENING AMONG MSM IN HIV CARE

- Medical Monitoring Project, nationally representative sample of adults in HIV care

- 69% had been screened for syphilis in last year
- 43% had been screened for CT/GC

% of sexually active HIV+ MSM screened for STIs

Mattson, 2016 CID

HIGH % OF PHARYNGEAL AND RECTAL CT/GC ASSOCIATED WITH NEGATIVE URINE TEST, STD SURVEILLANCE NETWORK (N=21994)

Patton et al CID 2014
HIGH % OF PHARYNGEAL AND RECTAL CT/GC ASSOCIATED WITH NEGATIVE URINE TEST, STD SURVEILLANCE NETWORK (N=21994)

Between 70-90% of infections would be missed by only screening with urine

SELF-COLLECTED RECTAL/PHARYNGEAL TESTING

- Highly acceptable, similar performance compared to clinician-collected specimens
- Self-collection can be performed at laboratory along with blood draw/urine collection or in the exam room before/after the provider visit
- May save patient an office visit
- Saves the provider time

Van der helm, 2009, STD; Sexton, 2013 J Fam Pract; Dodge, 2012 Sex Health Freeman 2011, STD; Alexander 2008, STI; Moncada 2009, STD
PATIENT SELF-COLLECTION INSTRUCTIONS

Step 1.
Open kit and remove tube and package with green writing. Remove the swab with the blue shaft. USE BLUE SHAFT SWAB ONLY.

Step 2.
Instruct patient to open mouth widely. Be sure to make good contact with 5 key areas of the throat (See below).

Step 3.
Remove cap from test tube. Place swab in test tube. Do not puncture the foil cap. Break swab shaft at the azote mark.

Step 4.
Put cap back tightly on test tube to prevent any leaking. Try not to splash the liquid out the tube.

Step 5.
Discard wrapper and unused swab. Wash your hands.

CT/GC TREATMENT
CHLAMYDIA TREATMENT

**ADOLESCENTS AND ADULTS**

**Recommended regimens (non-pregnant):**
- Azithromycin 1 g orally in a single dose
- Doxycycline 100 mg orally twice daily for 7 days

**Recommended regimens (pregnant***):
- Azithromycin 1 g orally in a single dose
- Amoxicillin 500 mg po TID x 7 days

* Test of cure at 3-4 weeks only in pregnancy

CDC 2015 STD Treatment Guidelines [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)

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**CHLAMYDIA TREATMENT**

**Alternative Regimen (non-pregnant):**
- Doxycycline (delayed release) 200 mg QD x 7 d
  - Equally efficacious to doxycycline BID, ↓ GI side effects
  - More $$$

**Moved to Alternative Regimen (pregnant***):
- Amoxicillin 500 mg po TID x 7 days
  - CT persistence documented in vitro after treatment prompted removal from recommended to alternate

CDC 2015 STD Treatment Guidelines [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)
AZITHROMYCIN vs. DOXYCYCLINE FOR TREATMENT OF UROGENITAL CT

- RCT comparing azithromycin with doxycycline
- Directly observed treatment of CT among teens in correctional facilities
- Measured treatment failure at 28 days after treatment initiation
  - Treatment failure determined on basis of NAAT, sexual history, and genotyping of CT strains
- Results: (N=155 in each group)
  - Azithromycin 97% effective
  - Doxycycline 100% effective


IS AZITHRO ADEQUATE TREATMENT FOR RECTAL CHLAMYDIA INFECTION?

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Repeat positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM in Australia</td>
<td>Azithro 1 g</td>
<td>13%</td>
</tr>
<tr>
<td>(N=85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM in Seattle</td>
<td>Azithro 1 g</td>
<td>22%</td>
</tr>
<tr>
<td>(N=407)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=95)</td>
<td>Doxy 100 BID x 7</td>
<td>8%</td>
</tr>
</tbody>
</table>

GONORRHEA DUAL THERAPY
UNCOMPPLICATED GENITAL, RECTAL, OR PHARYNGEAL INFECTIONS

Ceftriaxone 250 mg IM in a single dose

Azithromycin 1 g orally (preferred)
or
Doxycycline 100 mg BID x 7 days

PLUS*

• Regardless of CT test result

CDC 2015 STD Treatment Guidelines, www.cdc.gov/std/treatment

GONORRHEA TREATMENT ALTERNATIVES
ANOGENITAL INFECTIONS

ALTERNATIVE CEPHALOSPORIN:
❖ Cefixime 400 mg orally once
   PLUS
❖ Azithromycin 1 g (preferred)

IN CASE OF SEVERE ALLERGY:

Gentamicin 240 mg IM + azithromycin 2 g PO
OR
Gemifloxacin 320 mg orally + azithromycin 2 g PO

CDC 2015 STD Treatment Guidelines www.cdc.gov/std/treatment
GONORRHEA TREATMENT ALTERNATIVES
PHARYNGEAL INFECTIONS

“Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections...any person with pharyngeal gonorrhea who is treated with an alternative regimen should return 14 days after treatment for a test-of-cure using either culture or NAAT. If the NAAT is positive, effort should be made to perform a confirmatory culture before retreatment.”

https://www.cdc.gov/std/tg2015/gonorrhea.htm

<table>
<thead>
<tr>
<th></th>
<th>Gentamicin Regimen</th>
<th>Gemifloxacin Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>IM or IV</td>
<td>Oral</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
<td>37%</td>
</tr>
<tr>
<td>Vomiting (&lt;1 hour)</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Availability</td>
<td>OK</td>
<td>FDA reported shortage in May 2015</td>
</tr>
<tr>
<td>Volume</td>
<td>Need 6 cc (40mg/cc)</td>
<td></td>
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</table>
ANTIBIOTIC-RESISTANT GONORRHEA

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Priority 1: CRITICAL
- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH
- Enterococcus faecium, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter, fluoroquinolone-resistant
- Salmonella spp., fluoroquinolone-resistant
- Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM
- Streptococcus pneumoniae, penicillin-non-susceptible
- Haemophilus influenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant

GC ANTIBIOTIC RESISTANCE DEVELOPMENT OVER TIME

1930s: Introduction of sulfonamide antimicrobials to treat GC

1940s: Due to increasing resistance, sulfonamides no longer recommended for GC treatment; penicillin becomes treatment of choice

1940s: Due to increasing resistance, penicillin and tetracycline no longer recommended to treat GC

1980s: Fluoroquinolones become predominant treatment

1980s: Ceftriaxone no longer recommended as first-line regimen, leaving ceftriaxone-based dual treatment as last recommended treatment

2007: Fluoroquinolones no longer recommended; cephalosporins (incl. injectable ceftriaxone and oral cefixime) become backbone of GC treatment

2015: Ceftriaxone plus azithromycin is the only recommended treatment for treating GC

Slide courtesy of Dr. Heidi Bauer
ISOLATES WITH PENICILLIN, TETRACYCLINE, AND/OR CIPROFLOXACIN RESISTANCE, GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP), 2016

NOTE: PenR = penicillinase-producing Neisseria gonorrhoeae and chromosomally-mediated penicillin-resistant N. gonorrhoeae; TetR = chromosomally- and plasmid-mediated tetracycline-resistant N. gonorrhoeae; and QRNG = quinolone-resistant N. gonorrhoeae.

% OF ISOLATES WITH ELEVATED CEFTRIAXONE MICS (≥0.125 MG/ML) AND ELEVATED CEFIXIME MICS (≥0.25 MG/ML), GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP), 2006–2016

US: 0.8%
EU: 4.5%
China: 21%

Gonorrhea outbreak in Hawaii shows increased antibiotic resistance

By Susan Scutti, CNN
Updated 10:50 AM ET, Thu September 22, 2016


The Hawaii DOH has identified 7 cases of gonorrhea infection yielding isolates with uncommon antimicrobial susceptibility testing (AST) profiles, including very high azithromycin minimum inhibitory concentrations (MICs), alert-value ceftriaxone MICs, and elevated MICs for 5 other antibiotics.

<table>
<thead>
<tr>
<th>Minimum Inhibitory Concentrations, µg/mL</th>
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<tbody>
<tr>
<td>azithromycin</td>
</tr>
<tr>
<td>1 &gt; 256</td>
</tr>
<tr>
<td>2 &gt; 256</td>
</tr>
<tr>
<td>3 &gt; 256</td>
</tr>
<tr>
<td>4 &gt; 256</td>
</tr>
<tr>
<td>5 &gt; 256</td>
</tr>
<tr>
<td>6 &gt; 256</td>
</tr>
</tbody>
</table>

Katz CID 2017
GONORRHEA HAS REACHED NORTH AMERICA

Emerging Infectious Diseases, Vol 24 (2), February 2018

RECENT HIGH DOSE CEFTRIAXONE TREATMENT FAILURE IN UK

- Heterosexual male with sexual exposure in SE Asia
- Isolate with:
  - Ceftriaxone MIC=0.5
  - Azithromycin MIC>256
  - “Susceptible to Spectinomycin”
  - Ertapenem MIC =0.032
- Treated with ceftriaxone 1g
- Urine NAAT neg, Throat still positive
- Retreatment initiated with ertapenem
HOW MANY CASES IN THE US?

CDC has not received any reports of verified clinical treatment failures to any cephalosporin in the United States.

* The use of dual therapy for the treatment of gonorrhea is important for two reasons: 1) to ensure clinical cure in this era of increasing antibiotic resistance, and 2) to prevent further development of resistance.

https://www.cdc.gov/std/gonorrhea/arg/basic.htm

STRENGTHENING US RESPONSE TO RESISTANT GONORRHEA (SURRG)

Slide courtesy Yesid Romero Romero, Hawaii SURRG

CASE: I’M NOT ANY BETTER

- 25 yr old MSM on PrEP presents with urethral discharge x 2 days
  - urine GC positive / CT negative
  - Treated with ceftriaxone 250 mg IM and azithromycin 1g (directly observed therapy)

- Returns 1 week later, with persistent discharge visible on exam.
- He denies any interim sexual contact

POLL: WHAT DO YOU DO NEXT?

A) Panic
B) Call the health department
C) Repeat treatment with gentamicin 240 mg IM and azithromycin 2 g orally
D) Get a culture of the discharge
E) Get a urine NAAT for GC
F) All of the above except choice A
SUSPECTED GC TREATMENT FAILURE

TEST WITH CULTURE AND NAAT:
- If GC culture not available, call DOH

REPEAT TREATMENT:
- Gemifloxacin 320 mg + AZ 2g OR Gentamicin 240 mg IM + AZ 2g
- If reinfection suspected, repeat treatment with CTX 250 + AZ 1g

REPORT:
- To DOH within 24 hours

TEST AND TREAT PARTNERS:
- Treat all partners in last 60 days with same regimen

TEST OF CURE (TOC):
- TOC 7-14 days with culture (preferred) and NAAT

ANTIBIOTICS IN THE PIPELINE

- Solithromycin: novel oral fluoroketolide
  - Phase 2 trial (1200 mg and 1000 mg) GC treatment
    - 100% cured (neg culture) with either dose
    - GI side effects common and dose-related
  - Phase 3 trial underway

- Drugs in Development
  - Zoliflodacin (ETX0914/AZD0914)
  - Topoisomerase II inhibitor (spiropyrimidinetrione)
  - Activity against NG isolates with ciprofloxacin resistance and reduced susceptibility to extended-spectrum cephalosporins

Hook, EW et al. CID 2015.
Alm RA, Antimicrob Agents Chem. 2015
PARTNER MANAGEMENT

- Clinical evaluation is first-line option
  - Partner should be examined, counseled, tested and treated for STD(s) of exposure
- Expedited partner therapy (EPT) / patient-delivered partner therapy (PDPT) is an acceptable alternative
CT/GC PARTNER MANAGEMENT:
ALL SEXUAL CONTACTS IN PAST 60 DAYS NEED TREATMENT

Expedited partner treatment (EPT)

Patient referral

- Suggest patient bring partner to clinic for concurrent treatment (“CPPT”)
- Ask patient to notify partner and ensure treatment
- Internet-based anonymous notification

Health department referral

EPT: LEGAL STATUS IN U.S.

**PDPT Effectiveness in Randomized Controlled Trials**

Reduces reinfection with chlamydia & gonorrhea, but not trichomonas

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia</th>
<th>Chlamydia or Gonorrhea</th>
<th>Trichomonas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent re-infected at follow up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kissinger et al, 1998</td>
<td>22%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Schillinger et al, 2003</td>
<td>15%</td>
<td>12%</td>
<td>9.4%</td>
</tr>
</tbody>
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**CASE: I’M NOT ANY BETTER**

- 20 yr old female presented with yellowish vaginal discharge and cervicitis 2 weeks ago.

- You treated empirically for chlamydia with azithromycin (directly observed her taking it), her vaginal swab was + for CT, neg for GC

- Today she says her discharge went away a few days after treatment, but then it returned
POLL: WHAT DO YOU DO NEXT?

A) Repeat azithromycin 1 g in a single dose
B) Give doxycycline 100 mg BID x 7 days
C) Give moxifloxacin 400 mg daily x 7 days (cervicitis treatment failure)
D) Get more sexual history
E) Throw up your hands and say, “I’m sorry, I give up”

RETESTING FOR REPEAT GC/CT INFECTION
REPEAT CHLAMYDIAL INFECTION IS COMMON AMONG FEMALES


REINFECTION IS DANGEROUS

2\textsuperscript{nd} infection:
• 4x risk of PID
• 2x risk of ectopic pregnancy

3+ infections:
• 6x risk of PID
• 5x risk of ectopic pregnancy

Prepared by: CDPH STD Control Branch
HOW SOON CAN I RETEST?

- Need to wait at least 3 weeks for CT to clear
- GC clearance within 1-2 weeks (2 weeks for pharyngeal infection)
- 3 months is the target, but retest opportunistically whenever patient returns in the next 1-12 months
- Test of cure (TOC) not routinely indicated
  - Exception: pregnancy

*CDC 2015 STD Tx Guidelines, www.cdc.gov/std/treatment*

TAKE HOME POINTS

- Up and Up: ~7% increases in CT, ~19% increases GC over prior year
- STI testing at extragenital sites is key—self collected swabs can help improve screening rates
- *N. gonorrhoeae* azithromycin resistance increasing, a few new treatment options in the pipeline
- Expedited partner treatment helpful at reducing reinfections with CT/GC
- Remember to retest at 3 months after treatment (anytime after 3 weeks also ok).
STD CLINICAL CONSULTATION NETWORK (STDCCN)

- Provides STD clinical consultation services to healthcare providers nationwide (1-5 days depending on urgency)

- Your consultation request is linked to a CDC-funded STD Prevention Training Center’s expert faculty

www.STDCCN.org

THANK YOU
Any burning questions?