California Gonorrhea Treatment Guidelines

These guidelines were developed by the California Department of Public Health (CDPH) Sexually Transmitted Diseases (STD) Control Branch in conjunction with the California STD Controllers Association, and the California STD/HIV Prevention Training Center

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Summary Treatment Recommendations

DUAL ANTIBIOTIC THERAPY

Dual antibiotic therapy is now recommended for all suspected and confirmed cases of gonorrhea of the cervix, urethra, rectum, and pharynx **regardless of chlamydia test result.**

Antibiotic 1		Antibiotic 2
Ceftriaxone 250 mg intramuscularly (IM) in a single dose	**PLUS**	**Azithromycin** 1 g orally in a single dose (preferred) *OR* **Doxycycline** 100 mg orally twice daily for 7 days

- If treatment with ceftriaxone is not an option, cefixime 400 mg orally in a single dose PLUS azithromycin or doxycycline is an alternative treatment for cervical, urethral, or rectal gonorrhea.
- Cefixime should not be used for treatment of pharyngeal gonorrhea.

PELVIC INFLAMMATORY DISEASE (PID)

- Recommended outpatient treatment includes a parenteral cephalosporin (e.g., ceftriaxone), plus doxycycline and metronidazole (if bacterial vaginosis is present or cannot be ruled out).

TREATMENT IN CEPHALOSPORIN-ALLERGIC PATIENTS

- Azithromycin 2 g orally in a single dose may be used to treat cervical, urethral, rectal, or pharyngeal gonorrhea in patients with cephalosporin allergy or severe penicillin allergy.
- Routine use of azithromycin alone should be avoided due to evidence of emerging resistance.
- Fluoroquinolones (e.g., ciprofloxacin) should not be used for treatment due to high levels of antibiotic resistance.

PARTNER MANAGEMENT

- All partners within the past 60 days should be tested and empirically treated with a recommended antibiotic regimen.
- If the patient's last sexual contact was more than 60 days ago, the most recent partner should receive testing and empiric treatment.

PERFORMING A TEST OF CURE (TOC)

- A test of cure (TOC) should be performed routinely at 7 days after treatment: (1) for all pregnant women with gonorrhea, (2) for patients treated with antibiotics regimens that are not recommended (e.g., fluoroquinolones), and (3) for cases of suspected treatment failure.
- A TOC should be considered at 7 days after treatment for gay men and other men who have sex with men (MSM) who have been treated with alternative regimens (i.e., cefixime plus azithromycin or doxycycline or azithromycin monotherapy) because MSM are at higher risk of infection with cephalosporin-resistant gonorrhea.
- Ideally, TOC should be performed using culture. Nucleic acid amplification tests (NAATs) are acceptable as a second choice. A positive NAAT TOC alone at 7 days after treatment may not represent a true treatment failure. Please refer to "Performing a Test of Cure" (p. 8) for instructions.

SUSPECTED CEPHALOSPORIN TREATMENT FAILURE

Treatment failure should be suspected if: (1) symptoms persist or recur following initial antibiotic therapy, or (2) a TOC culture performed 7 days or more after treatment is positive, or (3) a TOC NAAT is persistently positive 14 days or more after treatment.

- Consult www.std.ca.gov for the latest gonorrhea treatment failure guidelines.
- Obtain specimens for a nucleic acid amplification test (NAAT) and culture at sites of sexual exposure (i.e., genital, rectal, pharyngeal). If gonorrhea culture is not available locally, contact the California STD Control Branch clinician warm line at (510) 620-3400, Monday-Friday, 8am-5pm for assistance.
- Re-treat the patient with ceftriaxone 500 mg IM plus azithromycin 2 g orally in a single dose.
- Inform your local health department of the case within 24 hours. Please also call the California STD Control Branch clinician warm line at (510) 620-3400.
- Ensure that all of the patient's partners in the last 60 days are notified and referred for testing and empiric treatment with ceftriaxone 500 mg IM plus azithromycin 2 g orally in a single dose. Your local health department may be able to provide assistance with partner notification.
- Instruct the patient to abstain from oral, vaginal, or anal sex until one week after the patient and all of his/her partners are treated and all symptoms have resolved.
- Ask the patient to return for a test of cure 7 days after treatment with NAAT and culture.

RETESTING FOR REPEAT INFECTION

- All patients with gonorrhea should be retested for repeat infection approximately 3 months after treatment.
- Retesting can be performed opportunistically any time the patient returns for care during 1-12 months after treatment.

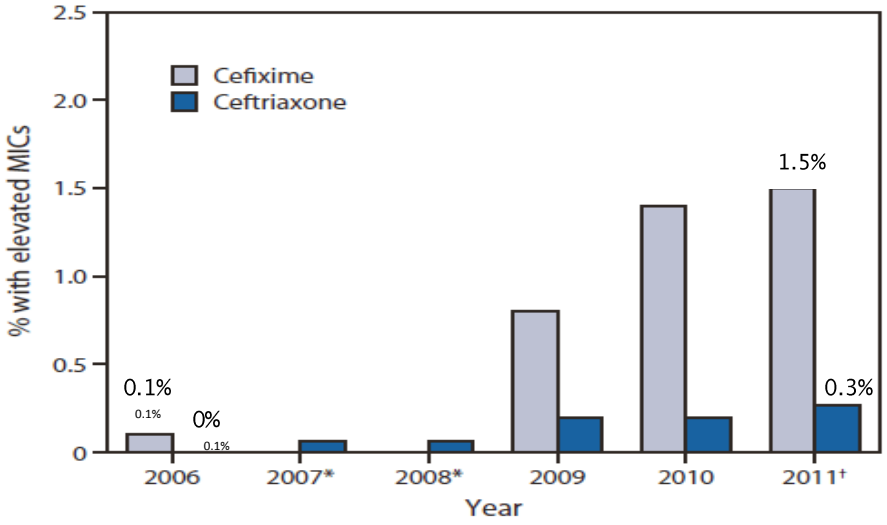
I. Reduced Susceptibility of Gonorrhea to Cephalosporins

The Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) published on August 10, 2012 reported further decline in cephalosporin susceptibility among isolates of *Neisseria gonorrhoeae* in the United States, particularly in California and other western states.[1] The isolates were obtained through the national Gonococcal Isolate Surveillance Project (GISP), a CDC sponsored, sentinel surveillance system that monitors antimicrobial susceptibilities in *N. gonorrhoeae* through testing of male urethral gonococcal cultures at STD clinics throughout the United States.

Antibiotic susceptibility was measured by the minimum inhibitory concentration (MIC), or the minimum concentration of antibiotic that inhibits visible bacterial growth. Cephalosporin MIC data from January through August 2011 was compared to the data from previous years. The CDC utilized thresholds for cefixime MICs ≥0.25 μg/mL and ceftriaxone MICs ≥0.125 μg/mL as representative of elevated MICs for surveillance purposes; actual MIC thresholds for cefixime and ceftriaxone resistance in *N. gonorrhoeae* have not yet been defined.

The data in the figure and table that follow demonstrate increases in the percentage of gonococcal isolates with elevated cephalosporin MICs observed both nationally and by region and subpopulation. From 2006 to 2011, the proportion of isolates with elevated cefixime MICs increased from 0.1% to 1.5%; the proportion with elevated ceftriaxone MICs increased from 0% to 0.3%. (Figure 1) The greatest increases were observed in the West and among men who have sex with men (MSM). (Table 1)

FIGURE 1. Percentage of urethral *Neisseria gonorrhoeae* isolates (n = 32,794) with elevated cefixime MICs (≥0.25 μg/mL) and ceftriaxone MICs (≥0.125 μg/mL) — Gonococcal Isolate Surveillance Project, 2006–2011†



Abbreviation: MICs=minimum inhibitory concentrations.
*Cefixime susceptibility not tested during 2007–2008.
†January–August 2011.

TABLE 1. Percentage of urethral *Neisseria gonorrhoeae* isolates with elevated cefixime MICs (≥0.25 µg/mL), by region and gender of sex partner — Gonococcal Isolate Surveillance Project, 2006–2011

Region	2006		2011	
	%	(95% CI)	%	(95% CI)
West* (total)	**0.2**	**(0.1–0.4)**	**3.2**	**(2.3–4.2)**
MSM	0.1	(0.0–0.6)	4.5	(3.1–6.3)
MSW	0.2	(0.0–0.6)	1.8	(0.9–3.1)
Midwest†(total)	**0.0**	**(0.0–0.3)**	**0.6**	**(0.2–1.5)**
MSM	0.0	(0.0–2.8)	4.9	(1.4–12.2)
MSW	0.0	(0.0–0.3)	0.0	(0.0–0.6)
Northeast and South‡ (total)	**0.1**	**(0.0–0.3)**	**0.3**	**(0.1–0.8)**
MSM	0.6	(0.0–3.0)	1.5	(0.4–3.9)
MSW	0.0	(0.0–0.2)	0.1	(0.0–0.4)

Abbreviations: CI=confidence interval; MICs=minimum inhibitory concentrations; MSM=men who have sex with men; MSW=men who have sex exclusively with women.

*Includes data from Albuquerque, NM; Denver, CO; Honolulu, HI; Las Vegas, NV; Los Angeles, CA; Orange County, CA; Phoenix, AZ; Portland, OR; San Diego, CA; San Francisco, CA; and Seattle, WA.
†Includes data from Chicago, IL; Cincinnati, OH; Cleveland, OH; Detroit, MI; Kansas City, MS; and Minneapolis, MN.
‡Includes data from Atlanta, GA; Baltimore, MD; Birmingham, AL; Dallas, TX; Greensboro, NC; Miami, FL; New Orleans, LA; New York, NY; Oklahoma City, OK; Philadelphia, PA; and Richmond, VA

II. National Gonorrhea Treatment Guidelines

Given concerns over gonorrhea antimicrobial resistance and oral cephalosporin resistance in particular, the CDC 2010 STD Treatment Guidelines[2] have been updated to emphasize the importance of dual antibiotic treatment for all gonorrheal infections with ceftriaxone plus azithromycin or doxycycline. Azithromycin is preferred over doxycycline for dual antibiotic treatment of gonorrhea; gonococcal isolates with elevated cefixime MICs demonstrate high rates of coexisting tetracycline resistance but azithromycin resistance is still rare.[1] National treatment recommendations are available at: www.cdc.gov/std/treatment.

III. California Gonorrhea Treatment Recommendations

The following recommendations are based on available data and the recent update to the 2010 CDC STD Treatment Guidelines.[1] Factors considered in developing these recommendations include therapeutic efficacy, side effects of particular agents, and concerns about emerging antimicrobial resistance. Clinics that are not currently delivering medications by IM injection should make every effort to establish protocols to deliver IM medications.

UNCOMPLICATED CERVICAL, URETHRAL, OR RECTAL GONORRHEA: Recommended Dual Antibiotic Therapy		
Antibiotic 1		**Antibiotic 2**
Ceftriaxone 250 mg IM in a single dose	**PLUS**	**Azithromycin** 1 g orally in a single dose (preferred) *or* **Doxycycline** 100 mg orally twice daily for 7 days
Note: • Dual therapy with a ceftriaxone **plus** azithromycin or doxycycline is recommended **regardless of the chlamydia test result.**		

UNCOMPLICATED CERVICAL, URETHRAL, OR RECTAL GONORRHEA: Acceptable Alternatives for Dual Antibiotic Therapy		
Antibiotic 1		**Antibiotic 2**
Cefixime 400 mg orally in a single dose *or* **Ceftizoxime** 500 mg IM in a single dose *or* **Cefoxitin** 2 g IM **plus** **Probenecid** 1 g orally in a single dose *or* **Cefotaxime** 500 mg IM in a single dose	**PLUS**	**Azithromycin** 1 g orally in a single dose (preferred) *or* **Doxycycline** 100 mg orally twice daily for 7 days
Note: • Injectable cephalosporins listed do not offer a therapeutic advantage over ceftriaxone.		

PHARYNGEAL GONORRHEA: Recommended Dual Antibiotic Therapy		
Antibiotic 1		**Antibiotic 2**
Ceftriaxone 250 mg IM in a single dose	**PLUS**	**Azithromycin** 1 g orally in a single dose (preferred) *or* **Doxycycline** 100 mg orally twice daily for 7 days
Note: • Oral cephalosporins should not be used for treatment of pharyngeal gonorrhea.		

GONORRHEA TREATMENT IN CEPHALOSPORIN-ALLERGIC PATIENTS: Uncomplicated cervical, urethral, rectal or pharyngeal gonorrhea
Azithromycin 2 g orally in a single dose
Notes: • Antibiotic desensitization can be performed but is impractical in most clinical settings • Due to emerging resistance[3], azithromycin should only be used in patients with cephalosporin allergy or significant IgE-mediated penicillin allergy (e.g., anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis). • Spectinomycin is efficacious for urogenital/rectal gonorrhea but is not available in the United States. • Fluoroquinolones (e.g., ciprofloxacin) should not be used for gonorrhea treatment.

GONORRHEA IN PREGNANCY: Recommended Dual Antibiotic Therapy Uncomplicated cervical, urethral, rectal or pharyngeal gonorrhea		
Antibiotic 1		**Antibiotic 2**
Ceftriaxone 250 mg IM in a single dose	**PLUS**	**Azithromycin** 1 g orally in a single dose
Notes: • Doxycycline is contraindicated in pregnancy. • In pregnant women with allergy to cephalosporins or significant anaphylactic (IgE-mediated) allergy to penicillin, azithromycin 2 g orally in a single dose may be considered. • A test of cure with a NAAT is recommended 3-4 weeks after treatment. • Retesting for repeat infection is recommended prior to delivery.		

IV. Pelvic Inflammatory Disease (PID) Treatment Recommendations

PELVIC INFLAMMATORY DISEASE: Recommended Antibiotics (IM/Oral)				
Antibiotic 1		**Antibiotic 2**		**Antibiotic 3**
Ceftriaxone 250 mg IM in a single dose *or* **Cefoxitin** 2 g IM with **Probenecid** 1 g orally in a single dose *or* **Other parenteral 3rd generation cephalosporin** (e.g., cefotaxime)	**PLUS**	**Doxycycline** 100 mg orally twice daily for 14 days	**PLUS**	**Metronidazole** 500 mg orally twice a day for 14 days (if bacterial vaginosis present or cannot be ruled out)

The updated CDC STD Treatment Guidelines recommend that fluoroquinolones not be used for PID treatment, leaving no solely oral therapeutic options available for PID. However, gonorrhea is not detected in the majority of PID cases in California, and PID can be caused by organisms other than STDs. In settings where IM medication is not available, fluoroquinolones may be considered alternative therapy for PID only if the risk of gonorrhea is low, a NAAT for gonorrhea is performed, and follow-up of the patient is likely. Regimens include levofloxacin 500 mg orally daily for 14 days or ofloxacin 400 mg orally twice daily for 14 days, plus metronidazole 500 mg orally twice a day for 14 days if bacterial vaginosis is present or cannot be ruled out.

Risk for gonorrhea should be considered low in the following women: 1) over 25 years of age, 2) in a monogamous relationship where the partner is not known to have other partners, and 3) no history of gonorrhea in the prior two years. Prevalence of gonorrhea is highest among African American women compared to other racial/ethnic groups, which should be considered when choosing the optimal regimen for PID.

If the test for gonorrhea is positive in a patient who received a fluoroquinolone-based regimen for PID, the patient should return to clinic to: 1) receive treatment with the recommended cephalosporin plus doxycycline regimen and 2) receive a test of cure with culture. A complete list of recommended and approved alternative treatments for PID is available at: www.cdc.gov/std/treatment.

Patients with PID should be reevaluated in 72 hours after initiation of therapy to monitor for clinical response. Further recommendations are available at: http://www.cdc.gov/std/treatment/2010/pid.htm

V. Partner Management

- The optimal management strategy for partners is a complete clinical evaluation, counseling, STD testing, and treatment.
- All partners of patients with gonorrhea within the past 60 days should be tested and empirically treated with a recommended antibiotic regimen. (See section III, p.5 for recommended regimens.)
- Presumptive antibiotic treatment of partners should occur immediately without waiting for laboratory confirmation of a positive result.
- If the patient's last sexual contact was more than 60 days prior to diagnosis, the most recent partner should receive testing and empiric treatment.
- If the patient's partners are unable or unlikely to seek care, then patient delivered partner therapy (PDPT) can be a useful alternative. Please refer to "Patient-Delivered Partner Therapy (PDPT) for Chlamydia, Gonorrhea, and Trichomoniasis: Guidance for Medical Providers in California", available at: www.std.ca.gov.
- For additional guidelines on partner management, please refer to "Best Practices for the Prevention and Early Detection of Repeat Chlamydial and Gonococcal Infections," available at: www.std.ca.gov.

VI. Performing a Test of Cure

CDC recommends that patients treated with alternative regimens (i.e., cefixime plus azithromycin or doxycycline, or azithromycin monotherapy) receive a test of cure (TOC) in 7 days; however implementing routine TOCs for these patients may be challenging. Notably there are no data on TOC positivity rates in the absence of persistent symptoms, and cost-effectiveness thresholds for TOC have not been established.

A TOC should be performed routinely:

- For all pregnant women diagnosed with gonorrhea
- For patients treated with antibiotic regimens that are not recommended (e.g., fluoroquinolones)
- In cases of suspected treatment failure

Health care providers should consider also performing TOCs for gay men and other men who have sex with me (MSM) who have been treated with alternative regimens (i.e., cefixime plus azithromycin or doxycycline or azithromycin monotherapy) because MSM are at higher risk of infection with cephalosporin-resistant gonorrhea.

Ideally, TOC should be performed using culture. Nucleic acid amplification tests (NAATs) are acceptable as a second choice. If a NAAT for gonorrhea is positive 7 days after initial treatment:

- Confirm positive NAAT with culture, if available.
- If the confirmatory culture is positive, the patient should be treated according to the most recent treatment failure guidelines. Antimicrobial susceptibility testing (AST) is recommended for all positive TOC cultures.

- If culture is not available and the patient agrees to abstain from sexual contact for 7 days, then the patient may be retested with a repeat NAAT in 7 days (14 days after initial treatment). If the NAAT is persistently positive, the patient should be treated according to the most recent treatment failure guidelines.
- If the patient cannot ensure abstinence from sexual contact for 7 days, the patient should be treated according to the most recent treatment failure guidelines.
- For the most recent treatment failure guidelines, see section VII, p. 10.

Because NAATs can detect DNA from potentially non-viable organisms, a positive gonorrhea NAAT at 7 days after treatment may not represent a true treatment failure. However, a study using an older NAAT technology demonstrated that the average time to negative NAAT after treatment was 3 days or less in both men and women with urogenital gonorrhea.[4] There are no published data on the time to negative NAAT for rectal or pharyngeal gonorrhea.

Chlamydia NAAT results may remain positive for up to 3 weeks after successful treatment; positive results before 3 weeks are not considered treatment failure and patients do not need to be re-treated.

For assistance or clinical consultation regarding TOC, please call the STD Warm Line at (510) 620-3400, Monday-Friday, 8am-5pm, and ask to speak with the clinician on call.

VII. Guidelines for Suspected Cephalosporin Treatment Failure

Gonorrhea treatment failure guidelines may change. For the most updated protocols for suspected treatment failures please refer to "California Gonorrhea Treatment Guidelines—Suspected Cephalosporin Treatment Failure" available at www.std.ca.gov

Treatment failure should be suspected if:

- Symptoms persist or recur following initial antibiotic therapy or
- A TOC culture performed 7 days or more after treatment is positive or
- A TOC NAAT is persistently positive 14 days or more after treatment

Original site of infection	Potential treatment failure symptoms
Urethra	Discharge, dysuria, pyuria (leukocyte esterase on urine dipstick, or ≥ 10 white blood cells per high power field on microscopy of urine sediment)
Cervix	Vaginal discharge, dysuria, postcoital spotting
Pharynx	Pharyngitis or odynophagia
Rectum	Discharge, pain, bleeding, pruritis, tenesmus, or painful defecation

For patients with suspected treatment failure, the following steps should be taken to ensure adequate testing, treatment, partner management, and follow up:

1. Obtain specimens for NAAT and culture at sites of sexual exposure (i.e., genital, rectal, pharyngeal). If gonorrhea culture is not available at your local laboratory, contact the California STD Control Branch clinician warm line at (510) 620-3400, Monday-Friday, 8am-5pm for assistance.
2. Re-treat the patient with ceftriaxone 500 mg IM plus azithromycin 2 g orally in a single dose.
3. Inform your local health department of the case within 24 hours. Please also call the California STD Control Branch clinician warm line at (510) 620-3400.
4. Ensure that all of the patient's partners in the last 60 days are notified and referred for testing and empiric treatment with ceftriaxone 500 mg IM plus azithromycin 2 g orally in a single dose. Your local health department may be able to provide assistance with partner notification.

5. Instruct the patient to abstain from oral, vaginal, and anal sex until one week after the patient and all of his/her partners are treated and all symptoms have resolved.

6. Ask the patient to return for a TOC one week after treatment with NAAT and culture.

Note: Susceptibility testing should be performed for gonococcal isolates found on a positive TOC culture, including cephalosporin, macrolide, tetracycline, and fluoroquinolone susceptibility. If local susceptibility testing is performed, the specimen (or aliquot of the specimen) should be preserved for future analysis in the event that decreased susceptibility is identified.

The above recommendations are meant for patients with treatment failure after dual therapy with ceftriaxone or cefixime. Patients with persistent symptoms or a positive TOC after treatment with azithromycin monotherapy or a non-recommended regimen (e.g. fluoroquinolones) should be treated with ceftriaxone 250 mg IM plus azithromycin 1g orally.

Reinfection should be suspected in a patient who reports interim sexual exposure to untreated or new sex partners. Patients with suspected reinfection should be treated with ceftriaxone 250 mg IM plus azithromycin 1 g orally.

VIII. Retesting for Repeat Infection

All patients with gonorrhea should be retested approximately three months following treatment for infection, as the rates of reinfection are elevated in this group of previously infected persons. Retesting is distinct from a test of cure, which is only recommended in specific clinical situations (see Section VI, p. 8 "Performing a Test of Cure"). Retesting can be performed opportunistically any time the patient returns for care during 1-12 months after treatment.

IX. Online Resources

1. California Department of Public Health, STD Control Branch: www.std.ca.gov
2. Centers for Disease Control and Prevention: www.cdc.gov/std
3. California STD/HIV Prevention Training Center: www.stdhivtraining.org

X. Further Information

Questions or concerns regarding these recommendations should be addressed to:

STD Control Branch
California Department of Public Health
510-620-3400 (ask to speak to the on-call clinician)

XI. References

1. Centers for Disease Control and Prevention. Update to CDC's *Sexually Transmitted Diseases Treatment Guidelines, 2010*: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections. *MMWR Morb Mortal Wkly Rep*. Aug 10 2012:61(31);590-594.
2. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* Dec 17 2010;59(RR-12): 49-55, 63-67.
3. Centers for Disease Control and Prevention. *Neisseria gonorrhoeae* with reduced susceptibility to azithromycin--San Diego County, California, 2009. *MMWR Morb Mortal Wkly Rep.* May 13 2011;60(18):579-581.
4. Bachmann LH, Desmond RA, Stephens J, Hughes A, Hook EW. Duration of persistence of gonococcal DNA detected by ligase chain reaction in men and women following recommended therapy for uncomplicated gonorrhea. *J Clin Microbiol.* Oct 2002;40(10):3596-3601.