



CALIFORNIA
STD/HIV PREVENTION
TRAINING CENTER

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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DISCLAIMER FOR PUBLIC HEALTH CLINICAL GUIDELINES

These guidelines are intended to be used as an educational aid to help clinicians make informed decisions about patient care. The ultimate judgment regarding clinical management should be made by the health care provider in consultation with their patient, in light of clinical data presented by the patient and the diagnostic and treatment options available. The California Department of Public Health disclaims all liability for the accuracy or completeness of these guidelines, and disclaims all warranties, express or implied. Further, these guidelines are not intended to be regulatory and not intended to be used as the basis for any disciplinary action against the health care provider.

Summary Treatment Recommendations

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 1g 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 may also be used for treatment of cervical, urethral, or rectal gonorrhea. Cefixime should not be used for treatment of pharyngeal gonorrhea.

For pelvic inflammatory disease, 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

A test of cure should be performed: (1) routinely in pregnant women with gonorrhea, (2) if antibiotics other than recommended or approved alternative regimens are used, or (3) in cases of suspected treatment failure.

SUSPECTED CEPHALOSPORIN TREATMENT FAILURE

- Consult www.std.ca.gov for the latest gonorrhea treatment failure guidelines.
- Perform a culture at exposed sites (e.g., pharynx, genital sites, rectum). **If gonorrhea culture is not available from the laboratory serving your clinic site, contact the California STD Control Branch clinician warm line at (510) 620-3400, Monday through Friday, 8:00a.m.-5:00 p.m. for assistance.**
- If the patient was already treated with ceftriaxone plus azithromycin and is still symptomatic, re-treat with ceftriaxone 500 mg IM **plus** azithromycin 2 g orally in a single dose.
- Inform your local public health department of the case within 24 hours, and if further consult desired, call the California STD Control Branch clinician warm line at (510) 620-3400.
- All sexual partners in the last 60 days should receive empiric treatment and testing.
- 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.
- Perform a test of cure 1 week after treatment, preferably with culture, or, if culture is not available, with a nucleic acid amplification test (NAAT).

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 July 8, 2011 reported decreased cephalosporin susceptibility among isolates of *Neisseria gonorrhoeae* in the United States, especially 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. The CDC utilized thresholds for cefixime MICs $\geq 0.25 \mu\text{g/mL}$ and ceftriaxone MICs $\geq 0.125 \mu\text{g/mL}$ as representative of elevated MICs for surveillance purposes; actual MIC thresholds for cefixime and ceftriaxone resistance in *N. gonorrhoeae* have not yet been defined.

Percentage of *N. gonorrhoeae* isolates with elevated cefixime or ceftriaxone MICs: Gonococcal Isolate Surveillance Project 2000-2010, n=5865

Geographic Area	% of isolates with Cefixime MIC* \geq 0.25 $\mu\text{g}/\text{mL}$		% of isolates with Ceftriaxone MIC \geq 0.125 $\mu\text{g}/\text{mL}$	
	2000	2010	2000	2010
National	0.2%	1.4%	0.1%	0.3%
California (Los Angeles, Orange, San Diego, and San Francisco Counties)	0.0%	4.5%	0.1%	0.6%
Population	2000	2010	2000	2010
Men who have sex with men	0.0%	4.0%	0%	0.9%
Men who have sex with women [†]	0.2%	0.3%	0.1%	0.1%

*Of isolates with cefixime MICs \geq 0.25 $\mu\text{g}/\text{mL}$, all exhibited resistance to both tetracycline and ciprofloxacin.

[†]No significant differences were seen in the proportion of isolates with elevated MICs among men who have sex with women between 2000 and 2010.

National gonorrhea resistance data can be found at: www.cdc.gov/std/gisp. Up-to-date California gonorrhea resistance data can be found at: www.std.ca.gov.

II. National Gonorrhea Treatment Guidelines

Given concerns over gonorrhea antimicrobial resistance, the CDC 2010 STD Treatment Guidelines have been changed to emphasize the importance of dual antibiotic treatment for all gonorrheal infections with ceftriaxone plus azithromycin or doxycycline.² According to the CDC, azithromycin is preferred over doxycycline for dual antibiotic treatment of gonorrhea due to high rates of co-existing tetracycline resistance among gonococcal isolates with elevated cefixime MICs.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 2010 CDC STD Treatment Guidelines. Factors considered in developing these recommendations include therapeutic efficacy (*see Attachment A, p. 11*), 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 (preferred) <i>or, if not an option</i> Cefixime 400 mg orally in a single dose	PLUS	Azithromycin 1 g orally in a single dose (preferred) <i>or</i> Doxycycline 100 mg orally twice daily for 7 days
Dual therapy with a cephalosporin 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
Ceftizoxime 500 mg IM in a single dose <i>or</i> Cefoxitin 2 g IM plus Probenecid 1g orally in a single dose <i>or</i> Cefotaxime 500 mg IM in a single dose <i>or</i> Cefpodoxime 400 mg orally in a single dose <i>or</i> Cefuroxime axetil 1 g orally in a single dose	PLUS	Azithromycin 1 g orally in a single dose (preferred) <i>or</i> Doxycycline 100 mg orally twice daily for 7 days
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 (preferred)	PLUS	Azithromycin 1 g orally in a single dose (preferred) <i>or</i> Doxycycline 100 mg orally twice daily for 7 days
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
Antibiotic desensitization can be performed but is impractical in most clinical settings
<ul style="list-style-type: none"> • 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		
Antibiotic 1		Antibiotic 2
Ceftriaxone 250 mg IM in a single dose	PLUS	Azithromycin 1 g orally in a single dose
<ul style="list-style-type: none"> • Doxycycline is contraindicated in pregnancy. • In pregnant women with allergy to cephalosporins or significant anaphylaxis-type (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 2010 CDC STD Treatment Guidelines continue to 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 would 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, 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 a test for gonorrhea is positive in a patient having received a fluoroquinolone for PID, a test of cure with bacterial culture should be performed and the patient should be re-treated with the recommended cephalosporin and doxycycline regimen. A complete list of recommended and approved alternative treatments for PID is available at: www.cdc.gov/std/treatment.

V. Partner Management

- 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.4 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.
- For 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 (click on "STD Guidelines")

VI. Performing a Test of Cure

A test of cure should be performed routinely in the following patients and clinical situations:

- Pregnant women diagnosed with gonorrhea at any stage of pregnancy (may use NAAT or culture)
- If antibiotics other than a recommended or approved alternative regimen are used (may use NAAT or culture)
- Suspected treatment failure (culture preferred over NAAT)

According to the CDC, clinicians caring for patients with gonorrhea in California, particularly men who have sex with men (MSM), may consider having these patients return one week after treatment for a test of cure, preferably with culture, or, if culture not available, with a NAAT.¹

Because NAATs can detect DNA from potentially non-viable organisms, a positive NAAT at seven 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 gonorrhea treatment was three days or less in both men and women.⁴

VII. Guidelines for Suspected Gonorrhea Treatment Failure

Please consult www.std.ca.gov for the most updated protocols for suspected treatment failures.

CASE DEFINITIONS

Suspected Treatment Failure: persistent or recurrent symptoms following antibiotic treatment in the absence of interim sexual exposure. Symptoms may be constant or intermittent.

Original site of infection	Potential treatment failure symptoms
Urethra	Discharge, dysuria, pyuria (positive leukocyte esterase on urine dipstick)
Cervix	Vaginal discharge, dysuria, post-coital spotting
Pharynx	Pharyngitis or odynophagia
Rectum	Discharge, pain, bleeding, pruritis, tenesmus, or painful defecation

Suspected Reinfection: persistent or recurrent symptoms in a patient who reports interim sexual exposure to untreated or new sex partners. Patients suspected of having a reinfection should be retreated with a recommended antibiotic regimen (see Section III, p. 4, “California Gonorrhea Treatment Recommendations”).

Confirmed Treatment Failure: positive test of cure (NAAT or culture) in the absence of reinfection (i.e., patient denies potential sexual re-exposure)

Suspected Treatment Failure: Testing and Treatment Protocol: If reinfection has been ruled out and treatment failure is still suspected, the following steps should be taken to ensure adequate testing, treatment, partner management, and follow up:

- Obtain a specimen for culture and antibiotic susceptibility testing at sites of sexual exposure (i.e., genital, rectal, pharyngeal). **If gonorrhea culture is not available from the laboratory serving your clinic site, contact the California STD Control Branch clinician warm line at (510) 620-3400, Monday through Friday, 8:00am-5:00pm for assistance.**
 - ❖ Susceptibility testing should be performed for gonococcal isolates found on a positive test-of-cure 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.
- If the patient was initially treated with the recommended ceftriaxone regimen, re-treat the patient with ceftriaxone 500 mg IM and azithromycin 2 g orally in a single dose.
- If the patient was initially treated with cefixime, other oral/injectable cephalosporin, or azithromycin monotherapy, re-treat the patient with ceftriaxone 250 mg IM and azithromycin 2 g orally in a single dose.

- Inform your local public health department of the case within 24 hours, and if further consult desired, 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 return to the clinic for empiric treatment with the same regimen as the index patient and STD testing at all sites of sexual exposure.
- 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.
- Ask patient to return for a test of cure one week after treatment. Test of cure should be performed using culture; however, if culture is not available, a NAAT can be used.

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 V, “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. Cephalosporin susceptibility among *Neisseria gonorrhoeae* isolates--United States, 2000-2010. *MMWR Morb Mortal Wkly Rep.* Jul 8 2011;60(26):873-877.
2. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* Dec 17 2010;59(RR-12): 49-55, 63-67.
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7. Hall C. Single-dose, oral cefpodoxime proxetil effective for treatment of uncomplicated urogenital and rectal *Neisseria gonorrhoeae*. *International Society for STD Research Meeting.* Seattle, WA; 2007.
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ATTACHMENT A.

Efficacy of Cephalosporins and Azithromycin in Treating Urogenital and Pharyngeal Gonococcal Infections[†]

Drug	Dose	Efficacy		Treatment Limitations
		Urogenital Infection	Pharyngeal Infection	
		Cure Rate, % (95% CI)	Cure Rate, % (95% CI)	
Ceftriaxone ^{5,6} (Rocephin)	250 mg (IM)	99.2 (98.8-99.5)	98.9 (94.2-100)	Intramuscular administration limits use in some settings.
Cefixime ^{5,6} (Suprax)	400 mg (PO)	97.5 (95.4-98.8)	92.3 (74.9-99.1)	Not recommended for treatment of pharyngeal infection due to lower cure rate than ceftriaxone.
Cefpodoxime ⁷ proxetil (Vantin)	400 mg (PO)	96.1 (93.1-100)	74.3 (56.8-87.5)	Not recommended for treatment of pharyngeal infection.
Cefuroxime ^{5,6} axetil (Ceftin)	1 gm (PO)	95.9 (94.3-97.2)	56.9 (42.2-70.7)	Not recommended for treatment of pharyngeal infection.
Azithromycin ^{5,6,8} (Zithromax; generic)	2 gm (PO)	99.2 (97.3-99.9)	95.2 (76.2-99.9)	Gastrointestinal side effects (nausea/vomiting) may occur. Concerns that widespread routine use may lead to rapid development of resistance.

IM-intramuscular

PO-by mouth

CI-confidence interval

[†]Data reflect efficacy for single antibiotic regimens only; there are no published data for comparative efficacy of dual antibiotic regimens versus single antibiotic regimens.

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