

# CALIFORNIA GONORRHEA TREATMENT GUIDELINES

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Developed in conjunction with the California Sexually Transmitted Diseases (STD)  
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# **CALIFORNIA GONORRHEA TREATMENT GUIDELINES**

California Department of Health Services  
Sexually Transmitted Diseases (STD) Control Branch

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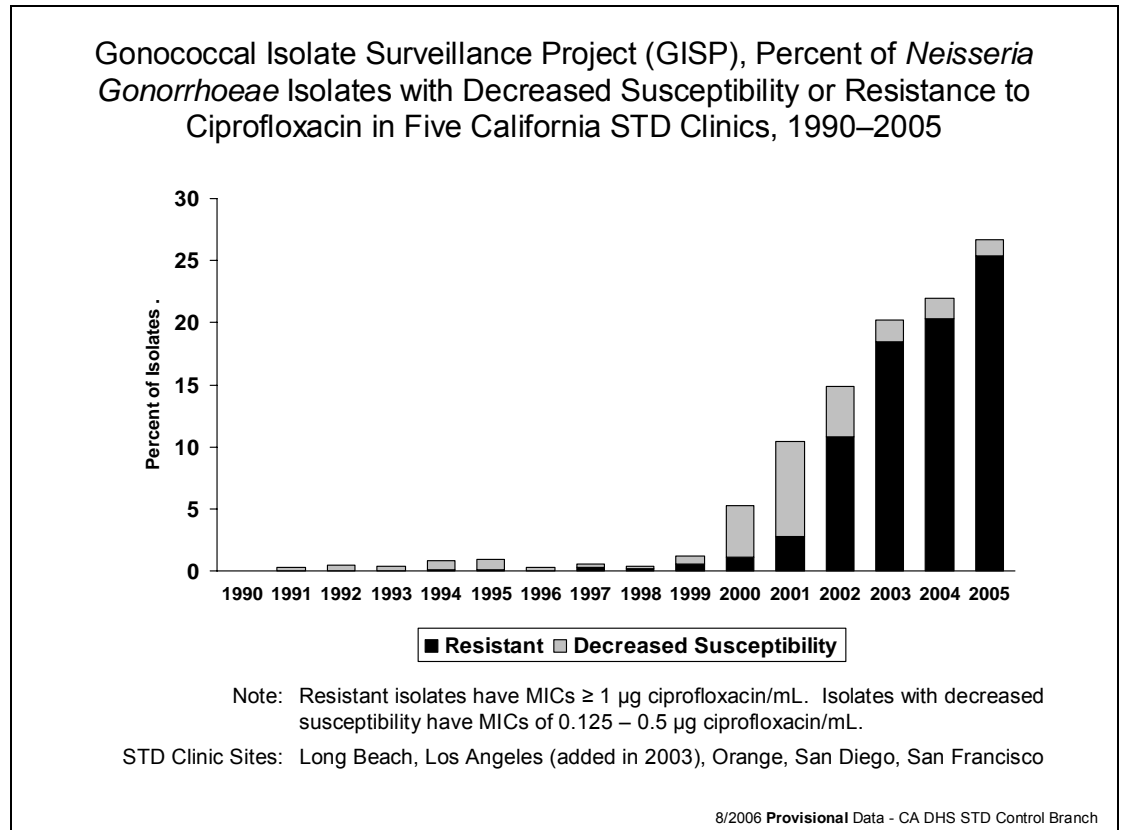
## **National Gonorrhea Treatment Guidelines**

STD treatment guidelines in 2006 from the Centers for Disease Control and Prevention (CDC) include fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin) as first-line therapy for uncomplicated gonococcal infections except in patients who: 1) are men who have sex with men (MSM); 2) have reported foreign travel (for either themselves or their partners); or 3) reside in any area in which decreased gonococcal susceptibility to such drugs is prevalent. To date, these areas include, but are not limited to, California, Hawaii, and other U.S. states, particularly those in the western United States; Asia and the Pacific; and multiple European regions, among other areas. National gonorrhea resistance data can be found at [www.cdc.gov/std/gisp](http://www.cdc.gov/std/gisp). Up-to-date California data and guidelines can be found at [www.std.ca.gov](http://www.std.ca.gov). CDC STD Treatment Guidelines 2006 may be viewed at: [www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment).

## **Increasing Fluoroquinolone Resistance in California**

Antimicrobial resistance surveillance in California found a prevalence of ciprofloxacin-resistant gonorrhea of more than 25 percent in 2005. These data are based on the California component of the national Gonococcal Isolate Surveillance Project (GISP), providing antibiotic susceptibility testing on gonococcal isolates from the first 25 male patients with urethral infections seen each month in sentinel STD clinics. The GISP surveillance system includes five sites in California: Long Beach, Los Angeles County, Orange County, San Diego County, and San Francisco County. Overall, levels of ciprofloxacin resistance were low through 1999 (less than 1 percent) and began rising sharply thereafter to 2.8 percent in 2001, 18.5 percent in 2003, and 25.4 percent in 2005. All California GISP sites have seen substantial increases in ciprofloxacin-resistant gonorrhea over this time period.

**Figure 1**



MIC: minimum inhibitory concentration

### California Gonorrhea Treatment Guidelines

The California Gonorrhea Treatment Guidelines were first released on May 24, 2002, and published in the July 2002 issue of the Medical Board of California *Action Report*. The recommendations were revised in June 2003, given developments in the manufacturing and distribution of medications named in the original release. Specifically, cefixime, the only oral cephalosporin listed as first-line treatment in California, ceased to be available from its U.S. distributor in November 2002. In 2004, the Food and Drug Administration (FDA) licensed an offshore manufacturer to distribute cefixime, but, to date, only a suspension form of the product is available, with release of a tablet form as yet uncertain. In addition, in 2006 the manufacturing of spectinomycin was discontinued in the United States, and future availability is uncertain.

In response to the persistent high level of fluoroquinolone-resistant gonorrhea in California and the lack of availability of cefixime and spectinomycin, the California

Department of Health Services' STD Control Branch and the California STD Controllers Association are issuing the following revised recommendations, based on available data and the newly released 2006 CDC STD Treatment Guidelines. Factors considered in developing these recommendations include therapeutic efficacy (see Table 1), cost and side effects of particular agents, and concerns about emerging antimicrobial resistance. For more information on treatment of gonorrhea, please refer to the 2006 CDC STD Treatment Guidelines ([www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)), as well as: <http://www.cdc.gov/std/treatment/Cefixime.htm> and <http://www.cdc.gov/MMWR/preview/mmwrhtml/mm5316a1.htm>.

### California Gonorrhea Treatment Recommendations

- Fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin) should not be used to treat gonorrhea in California, because of high levels of resistance.
- Routine, widespread use of azithromycin should be avoided for treatment of gonorrhea in California, due to mounting concerns about emerging resistance.
- Patients with gonorrhea should be co-treated for *Chlamydia trachomatis* unless this infection has been ruled out with a negative nucleic acid amplification test (NAAT) result (see section below on co-treatment for Chlamydia).

#### **CERVICAL, URETHRAL, AND RECTAL INFECTIONS – Recommended Antibiotics**

Recommended antibiotics for treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum include:

- ◆ **Ceftriaxone** 125 mg intramuscularly in a single dose;<sup>1</sup>  
OR
- ◆ **Cefixime** 400 mg orally in a single dose.<sup>2</sup>

<sup>1</sup> Based on the pharmacokinetics of ceftriaxone 125 mg, this is the preferred treatment for gonorrhea. Since the drug is packaged as a 250 mg vial, some clinicians in low-volume settings elect to use 250 mg, given product shelf-life. While 125 mg remains the recommended dose, use of 250 mg is acceptable.

<sup>2</sup> Cefixime suspension is available in the United States. The manufacturer, Lupin Ltd (phone: 800-826-9556), plans to release a tablet form of the drug, but availability has been delayed since 2004 and remains uncertain.

## CERVICAL, URETHRAL, AND RECTAL INFECTIONS – *Alternative Antibiotics*

Alternative antibiotic regimens for the treatment of uncomplicated gonococcal infections of the cervix, urethra, and rectum include:

- ◆ **Cefpodoxime** 400 mg orally in a single dose;<sup>3</sup>  
OR
- ◆ **Spectinomycin** 2 gm intramuscularly in a single dose.<sup>4</sup>

*Single-dose injectable cephalosporins (**Ceftizoxime** 500 mg intramuscularly, **Cefoxitin** 2 gm intramuscularly with **Probenecid** 1 gm orally, or **Cefotaxime** 500 mg intramuscularly) remain alternative options for treating gonorrhea but offer no advantage over other available options.*

## PHARYNGEAL GONORRHEA

When gonococcal infection of the pharynx is detected or suspected, an antimicrobial with demonstrated efficacy at this anatomic site should be used.

The recommended antibiotic for treatment of gonococcal infection of the pharynx is:

- ◆ **Ceftriaxone** 125 mg intramuscularly in a single dose.

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<sup>3</sup> A multicenter study in California recently assessed the efficacy of oral cefpodoxime for the treatment of uncomplicated gonorrhea; results are expected in early 2007. Some jurisdictions in California and elsewhere have begun using this oral agent routinely to treat uncomplicated gonorrhea at multiple anatomic sites, given small studies in the 1990s demonstrating efficacy exceeding 95 percent, despite the lower bound of the 95 percent confidence interval of efficacy just below 95 percent, or that required by CDC for recommendation of anti-gonococcal antimicrobials. See Table 1.

<sup>4</sup> While some non-expired local supplies remain available, U.S. manufacturing of spectinomycin ceased in January 2006. Negotiations are underway to re-initiate manufacturing and/or make offshore supplies available in the United States; however, to date, future availability of spectinomycin in the United States remains uncertain.

## GONORRHEA TREATMENT IN CEPHALOSPORIN-ALLERGIC PATIENTS

*Note: Since spectinomycin is no longer available in the United States, and all other recommended and alternative agents are cephalosporins, clinicians are challenged to treat patients who have cephalosporin allergy or significant, IgE-mediated penicillin allergy in which cross-reaction of penicillin with cephalosporins is a concern. The few available options include a number of important caveats:*

### CERVICAL, URETHRAL, AND RECTAL INFECTIONS

- ◆ Antibiotic desensitization followed by ceftriaxone or cefixime, as recommended by CDC but often is not feasible;  
OR
- ◆ **Azithromycin** 2 gm orally in a single dose with close clinical follow-up;  
*Note: judicious use of azithromycin is paramount because of mounting concerns about emerging resistance. Performing a test-of-cure (TOC) following use of azithromycin is prudent, given concerns about resistance;*  
OR
- ◆ **Spectinomycin** 2 gm intramuscularly in a single dose (not effective for pharyngeal gonorrhea).<sup>4</sup>

### PHARYNGEAL INFECTIONS

- ◆ Use of a recommended agent (e.g., ceftriaxone) following antibiotic desensitization protocol, as recommended by CDC, but often is not feasible;  
OR
- ◆ **Azithromycin** 2 gm orally in a single dose with close clinical follow-up and TOC, as discussed above.

## Pelvic Inflammatory Disease (PID) Treatment Recommendations

Treatment of PID is also challenging in California. The 2006 CDC STD Treatment Guidelines ([www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment)) recommend that fluoroquinolones not be used for PID treatment in California, leaving no oral PID options available. A number of factors raise serious concerns about timely treatment for many women diagnosed with PID when the risk of gonorrhea is low, if this recommendation is strictly followed for all PID cases in California: (1) gonorrhea is not detected in the majority of PID cases in California; (2) PID is not always a sexually transmitted infection; and (3) a fluoroquinolone regimen is commonly used to treat PID in California private practice settings where injectable cephalosporins are not readily available.

While treatment with ceftriaxone or ceftioxin/probenecid plus doxycycline is the

preferred regimen, treatment courses containing fluoroquinolones may be considered alternatives for PID when the risk of gonorrhea is low,<sup>5</sup> a NAAT for gonorrhea is performed, and follow-up of the patient is considered likely. Furthermore, if a test for gonorrhea is positive in a patient having received a fluoroquinolone, a TOC with the use of bacterial culture should be performed and the patient should be re-treated with the recommended cephalosporin/doxycycline regimen.

### **Chlamydia Co-Treatment Recommendations**

Treatment for co-infection with *Chlamydia trachomatis* in patients with gonorrhea continues to be recommended unless chlamydial infection has been ruled out with the use of sensitive test technology (i.e., NAAT). Recommended antibiotics for the treatment of chlamydial infection include:

- ◆ **Azithromycin** 1 gm orally in a single dose;
- OR
- ◆ **Doxycycline** 100 mg orally twice daily for seven days.

### **Gonorrhea Treatment in Pregnancy**

Pregnant women should be treated with a recommended or alternative agent listed above in the California Gonorrhea Treatment Guidelines. In women with allergy to cephalosporins or significant anaphylaxis-type (IgE-mediated) allergy to penicillin, a single 2 gm intramuscular dose of spectinomycin should be administered or, if unavailable, CDC recommends cephalosporin desensitization. Although no studies have evaluated the efficacy of a single 2 gm oral dose of azithromycin, if desensitization is not an option, this regimen may be considered (see risks noted above).

### **TOC Indications and Instructions**

Obtaining a TOC is important whenever regimens other than the recommended or alternative regimens listed above (i.e., ceftriaxone, cefixime, cefpodoxime, or spectinomycin for cervical, urethral, or rectal infection; or ceftriaxone for pharyngeal infection) are used or when treatment failure is suspected. Ideally, TOC should be performed with the use of a sensitive gonococcal culture method<sup>6</sup> approximately one week following treatment. If only a NAAT is available, TOC should be obtained no

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<sup>5</sup> Epidemiologic data in California suggests that the risk for gonorrhea in PID is low if the woman is over 25 years of age, in a monogamous relationship with a partner not known to have other partners, and has not had gonorrhea in the prior two years. In California, prevalence of gonorrhea is highest among African American women, compared to other racial and ethnic groups, which should be taken into consideration when choosing the optimal regimen for PID in these women.

<sup>6</sup> Sensitive gonococcal culture involves inoculation of modified Thayer-Martin medium (culture plates) at the time of specimen collection, with maintenance of plates under anaerobic conditions and/or prompt transport to the laboratory for proper incubation.

earlier than three to four weeks following treatment, to avoid a false-positive result due to retained gonococcal nucleic acid material following successful treatment. If clinicians encounter a treatment failure after any of the gonorrhea treatment regimens listed above, in the absence of re-exposure, all necessary steps should be taken to culture the organism.

For all TOC gonococcal isolates, resistance testing should be performed, specifically for fluoroquinolone, cephalosporin, and macrolide susceptibility. If local susceptibility testing is performed, the specimen (or aliquot of the specimen) should be held for future analysis in the event decreased susceptibility is identified. If local susceptibility testing is not available, the specimen should be forwarded to CDC, with the use of local and state public health laboratory specimen handling procedures.

### **Re-testing for Gonorrhea Infection**

All male and female patients with gonorrhea should be re-tested at three months following treatment for infection, as the rate of re-infection is elevated in this group of previously infected persons. Such re-testing is distinct from TOC, which is not routinely recommended. If a patient fails to return for evaluation at three months, he or she should be re-tested at the next clinical visit.

### **Further Information**

Questions or concerns regarding these recommendations should be addressed to:

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**Table 1: Efficacy of Oral Alternatives in Treating Urogenital and Pharyngeal Gonococcal (GC) Infections<sup>7</sup>**

Drug	Dose	Efficacy		Cost per dose	Limitations
		Urogenital Infection Cure Rate, % (95% CI)	Pharyngeal Infection Cure Rate, % (95% CI)		
Ceftriaxone (Rocephin)	125 mg (IM)	99.1 (98.7-99.8)	93.7 (84.5-98.2)	\$7.50	<i>Intramuscular administration limits use in some settings. Packaged as 250 mg vial.</i>
Cefixime (Suprax)	400 mg (PO)	97.7 (96.1-99.3)	100 (63.1-100)	\$21.00	<i>Currently available only as a suspension.</i>
Cefpodoxime proxetil (Vantin)	200 mg (PO)	96.5 (94.3-98.5)	78.9 (54.4-94.0)	\$5.50	<i>Clinical trials on pharyngeal GC included 19 males.</i>
Cefpodoxime proxetil (Vantin)	400 mg (PO)	100 (69.1-100)	no published data	\$11.00	<i>Clinical trial on urogenital GC included 10 patients. A multicenter study in California recently assessed the efficacy of oral cefpodoxime for the treatment of uncomplicated gonorrhea; results are expected in early 2007.</i>
Cefuroxime axetil (Ceftin)	1 gm (PO)	96.2 (94.8-97.5)	56.9 (43.3-70.5)	\$29.00	<i>Cure rate for pharyngeal GC is unacceptably low.</i>
Ceftibuten (Cedax)	400 mg (PO)	98.2 (93.6-99.8)	no published data	\$10.00	<i>Clinical trial on urogenital GC included men only.</i>
Azithromycin (Zithromax; generic)	2 gm (PO)	99.2 (97.2-99.9)	100 (82.3-100)	\$48.50	<i>High frequency of gastrointestinal side effects at dose required to treat gonorrhea. Concerns about that mechanism of resistance may lead to rapid development of resistance if used routinely.</i>

IM = intramuscular; PO = oral. Cost based on average wholesale price; actual cost depends on volume, packaging, and formulation. CI = Confidence Interval.

Prepared by California Department of Health Services.

<sup>7</sup> Moran, J.S. and W.C. Levine. *Drugs of choice for the treatment of uncomplicated gonococcal infections*. Clin Infect Dis 1995; 20 Suppl 1: p. S47-65, and from the CDC website (<http://www.cdc.gov/std/treatment/Cefixime.htm>).