State of California—Health and Human Services Agency
California Department of Public Health

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Dear STD Control Colleagues:

I am writing to bring your attention to recent changes in national guidelines for the treatment and management of gonorrhea (GC).

1. New GC treatment guidelines from the CDC

Since December 2010, the Centers for Disease Control and Prevention (CDC) has recommended that health care providers treat uncomplicated GC infections with dual antibiotic therapy: ceftriaxone 250 mg intramuscular (IM) *plus* azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days. The oral antibiotic cefixime at a dose of 400 mg with either azithromycin or doxycycline was also a recommended therapy if ceftriaxone was not an option.

In this week's Morbidity and Mortality Weekly Report (MMWR), CDC released new data indicating an increase in the proportion of gonococcal isolates tested through the Gonococcal Isolate Surveillance Project (GISP) with "alert values" to cephalosporin antibiotics including cefixime and ceftriaxone. The alert values serve as a warning sign that cephalosporin resistance may be developing. In 2011, the highest proportions of gonococcal isolates with elevated minimum inhibitory concentrations (MICs) to cefixime are in the west (3.2%) and among men who have sex with men (MSM) (3.8%). It is important to note that these are only a warning sign of resistance -- we have not yet seen cases of treatment failure due to cephalosporin resistance in the U.S.

The full report, "Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections" (MMWR Weekly, August 10, 2012 / 61(31); 590-594), is available online: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s_cid=mm6131a3_e. Other useful materials, including the CDC report "Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan" are also available online: www.cdc.gov/std/treatment.

Given these new data, **CDC has changed the status of oral cefixime from a recommended treatment to an alternative treatment.** Because IM

cephalosporins are less likely to induce resistance, dual therapy with ceftriaxone *plus* azithromycin or doxycycline is now the only recommended therapy for uncomplicated GC infections. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the advantages of single-dose therapy and the higher prevalence of tetracycline resistance. For patients allergic to cephalosporins, azithromycin 2 g orally in a single dose is still considered an alternative treatment regimen.

The CDC further recommends that patients treated with an alternative regimen receive a test of cure (TOC) in 7 days, ideally with culture, although nucleic acid amplification tests (NAATs) are acceptable as a second choice. If the NAAT is positive, a confirmatory culture is recommended. Antimicrobial susceptibility testing (AST) is recommended for all positive TOC cultures.

Recommendations that patients treated for GC should be retested 3 months after treatment have not changed.

2. Local challenges to new GC treatment guidelines

These new recommendations create a number of challenges for all of us:

- Availability of medications: Many medical practices do not currently have the ability to provide on-site IM treatment and may rely heavily on writing prescriptions for oral medications. These new guidelines favoring IM treatment for GC may unintentionally create barriers to timely treatment and may even reduce providers' willingness to screen for GC. At this time, patients who have been previously treated with cefixime plus azithromycin (or doxycycline) do not need to be brought back for repeat treatment, as data from well-designed clinical trials support the efficacy of these regimens in curing uncomplicated urogenital GC.

- Accessibility of GC culture: Although many laboratories and hospitals in California have the capacity to perform GC cultures and AST, most providers do not have access to culture plates or other suitable transport media for specimens. Providers will likely contact their local health department to request assistance in following CDC recommendations for culture testing. If you are unable to provide assistance, please call the STD Warm Line at 510-620-3400 and we will try to find solutions.

- TOC for patients treated with an alternative regimen, including dual treatment with cefixime and azithromycin: There are no data on positivity rates in the absence of persistent symptoms, and cost-effectiveness thresholds for TOC

have not been established; however, populations with the highest risk for developing cephalosporin resistance (e.g., MSM) may receive more benefit from TOC. Additionally, implementing TOC may also be hampered by the lack of reimbursement mechanisms. These factors should be considered prior to strongly promoting this recommendation.

Another concern with using NAATs for TOC at 7 days is the risk of false positives caused by residual nucleic acid. A single U.S. study using an older NAAT technology found that the median time to clearance for urogenital infections was 1 day for men and 2 days for women; the vast majority of cases cleared by 2 weeks (*Bachmann et al, J. Clin. Microbiol. 2002; 40: 3596-3601*). To my knowledge, no data have been published on rectal or pharyngeal GC infections. The uncertainty over the significance of a positive NAAT TOC will likely create some frustration among health care providers.

- Provision of expedited partner treatment (EPT): Because we have always advocated that EPT should be used as a last resort when partners cannot be brought to care, EPT using dual treatment with cefixime and azithromycin continues to be an important harm reduction strategy for getting partners treated. California EPT guidelines are available online: http://www.cdph.ca.gov/pubsforms/Guidelines/Documents/CA-STD-PDPT-Guidelines.pdf

3. Suspected GC treatment failure

This week's MMWR also provides recommendations for managing suspected treatment failures. In particular, the CDC recommends consulting specialists in how to manage suspected ceftriaxone treatment failures.

California recommendations have been available online since August 2011 and specifically address the management, including treatment of suspected ceftriaxone treatment failures: http://www.cdph.ca.gov/pubsforms/Guidelines/Pages/CAGuidelinesGonorrheaTxFailure.aspx

In brief, for patients in California with suspected cephalosporin treatment failure, 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 all sites of sexual exposure (i.e., genital, rectal, pharyngeal). If GC culture is not available at your local laboratory, contact the STD Warm Line at (510) 620-3400, M-F 8am-5pm for assistance.

- Retreat the patient with ceftriaxone 500 mg intramuscular (IM) and azithromycin 2 g orally in a single dose.
- Ensure that all of the patient's partners in the last 60 days receive testing and empiric treatment with ceftriaxone 500 mg IM and azithromycin 2 g orally in a single dose.
- 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.
- Ask the patient to return for a test of cure (TOC) one week after treatment, preferably with culture, or, if culture is not available, with a nucleic acid amplification test (NAAT).

It is important to also consider that patients with persistent or recurrent symptoms who report interim sexual exposure to untreated or new partners most likely have been reinfected, rather than experiencing a true treatment failure. Patients likely to have been reinfected should be retreated with the recommended antibiotic regimen.

Alternative treatments are available for patients with severe allergies or ongoing treatment failure. Please call the STD Warm Line (510) 620-3400 for consultation on challenging cases.

4. Implications and action steps

Despite the many challenges discussed above, the new GC treatment guidelines provide an important opportunity to educate providers about the ongoing threat of emerging cephalosporin resistance and the importance of using IM ceftriaxone plus azithromycin whenever possible. Further, providers need to be vigilant for treatment failures and follow current recommendations for managing and reporting suspected treatment failures. Local STD programs have a key role in educating providers.

In addition, local STD programs should monitor GC treatment practices and promote the use of IM ceftriaxone plus azithromycin. It may be necessary to identify local referral sources for IM treatment to ensure linkage to high quality care for patients with GC. Access to culture and AST is particularly important for suspected treatment failures. If you are unable to identify local capacity for culture and AST, please call the STD Warm Line at 510-620-3400 for assistance.

The California Gonorrhea Treatment Guidelines will be updated to reflect new national guidance and posted online:
http://www.cdph.ca.gov/pubsforms/Guidelines/Documents/CA-GC-Treatment-Guidelines.pdf

As the new director for the state STD prevention and control program, I want to make sure you know my “open door” policy. I am never too busy to hear your concerns or help you problem-solve the challenges you face. On behalf of all our staff, I want to reiterate our resolve to support you in any way we can. Please let me know if you have any questions or concerns.

Sincerely,

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