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**State of Wisconsin**

Department of Health Services

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To: Local Health Department Health Officers  
Physicians  
Physicians' Assistants  
Nurse Practitioners, and  
Providers of STD Treatment and Prevention Services

From: Jeffrey P. Davis, MD  
Chief Medical Officer and State Epidemiologist  
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RE: Recent Changes to the National Guidelines for the Treatment and Management of  
Gonorrhea

The recent updates to the Centers for Disease Control and Prevention (CDC) recommendations for treating gonococcal infections (CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. MMWR 2012;61:590-594) pose challenges to treatment of gonococcal infections in Wisconsin. Following is a summary of the updates to the CDC STD treatment guidelines and the implications these have regarding availability of recommended medications, accessibility to laboratory culture services, tests-of-cure and provision of expedited partner therapy (EPT).

**The updated treatment guidelines**

Since December 2010, the CDC has recommended that health care providers treat uncomplicated gonococcal infections (GC) with dual antibiotic therapy:

Ceftriaxone 250 mg intramuscular (IM)

**PLUS**

Azithromycin 1 g orally as a single dose, **or**

Doxycycline 100 mg orally twice daily for 7 days

This was recommended as the most reliably effective treatment for uncomplicated gonorrhea. A single dose of cefixime 400 mg orally with either azithromycin or doxycycline was also a recommended therapy if ceftriaxone was not an option.

Included in the recently published update to the CDC STD treatment guidelines were CDC Gonococcal Isolate Surveillance Project (GISP) data demonstrating an increase in the proportion of gonococcal isolates with "alert values" to cephalosporin antibiotics including cefixime and ceftriaxone. The alert values serve as a warning that cephalosporin resistance among isolates of

*Neisseria gonorrhoeae* may be developing. Notably, these constitute only a warning of emerging antibiotic resistance. There have been no reports of treatment failure caused by cephalosporin resistance that has occurred in the United States. In Wisconsin, among 729 isolates of *N. gonorrhoeae* tested in the City of Milwaukee Health Department, Public Health Laboratory during January 2010-June 2012 (175 isolates tested in 2010; 360 tested in 2011; 194 tested in 2012), no isolates were detected to have elevated minimum inhibitory concentrations (MICs) to cefixime.

Attendant to these recently published GISP data, the CDC has revised the recommended treatment of GC. The CDC no longer recommends cefixime at any dose as a first-line regimen for treatment of GC infections. However, if cefixime is used as an alternative treatment agent, the patient should return in one week for a test-of-cure (TOC) at the site of infection. Because IM cephalosporins are less likely to induce antibiotic resistance, dual therapy with **ceftriaxone plus azithromycin or doxycycline is now the only recommended therapy for uncomplicated GC**. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the advantages of single-dose therapy and the greater prevalence of tetracycline resistance among isolates of *N. gonorrhoeae* (GISP % of isolates with MIC  $\geq 2.0$   $\mu\text{g/mL}$  is high but stable: 20.6% in 2006, 21.6% in 2011) compared to azithromycin (GISP % of isolates with MIC  $\geq 2.0$   $\mu\text{g/mL}$  is high but stable: 0.2% in 2006, 0.3% in 2011). For patients with severe cephalosporin allergy, CDC recommends azithromycin 2 g in a single oral dose plus a TOC in one week.

Tests-of-cure (TOC): The CDC recommendations that **patients treated with an alternative regimen receive a TOC in 7 days**, ideally with culture or with a nucleic acid amplification test (NAAT) if culture is not readily available. If the NAAT is positive, a confirmatory culture is recommended and should be aggressively pursued. All isolates from positive TOCs should have phenotypic antimicrobial susceptibility testing (AST).

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

### **Local challenges to new GC treatment guidelines**

These new recommendations create multiple challenges for all of us:

Availability of medications: Some medical practices currently do not provide on-site IM treatment and may rely 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, because data from well-designed clinical trials support the efficacy of these regimens in curing uncomplicated urogenital GC.

Accessibility of *N. gonorrhoeae* culture: Although some laboratories and hospitals have the capacity to perform *N. gonorrhoeae* cultures and AST, most providers do not have access to culture plates or other suitable transport media for specimens. Providers can contact the Wisconsin Division of Public Health (WDPH), Sexually Transmitted Disease (STD) Control

Section, at (608) 266-7945 to request assistance in following CDC recommendations for culture testing.

TOC for patients treated with an alternative regimen, including dual treatment with cefixime and azithromycin: There are no data regarding TOC 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., men having sex with men) 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 regarding use of NAATs for TOC at 7 days is the risk of false positives caused by residual nucleic acid. Results of a single U.S. study using older NAAT technology demonstrated the median time to clearance for urogenital infections was 1 day for men and 2 days for women; the vast majority of infections cleared by 2 weeks (Bachmann et al, J Clin Microbiol 2002;40:3596-3601). Uncertainty regarding the significance of a positive NAAT TOC will likely be associated with some frustration among health care providers, please call WDPH STD Control Section at (608) 266-7945 with questions.

Provision of expedited partner therapy (EPT): EPT is a partner management strategy, to be used when a partner is unable or unlikely to seek prompt clinical services. EPT using dual treatment with cefixime and azithromycin continues to be an important harm reduction strategy for getting partners' treated. Wisconsin EPT guidelines are available online: <http://www.dhs.wisconsin.gov/publications/P0/P00253.pdf>

### **Suspected GC treatment failure**

The updated treatment guidelines also provide recommendations for managing suspected treatment failures. Particularly, the CDC recommends consulting specialists regarding how to manage suspected ceftriaxone treatment failures.

Briefly, for patients in Wisconsin with suspected cephalosporin treatment failure, adherence to the following steps will help ensure adequate testing, treatment, partner management and follow up:

- Obtain specimens 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, please contact the WDPH STD Control Section at (608) 266-7945.
- Retreat the patient with ceftriaxone 250 mg intramuscular (IM) and azithromycin **2 g** orally in a single dose. (*Please note that re-treatment for suspected GC treatment failure requires **2g**, NOT 1g of azithromycin*).
- Alternative treatments are available for patients with severe allergies or ongoing treatment failure.
- Ensure that all of the patient's partners during the last 60 days receive testing and empiric treatment with ceftriaxone 250 mg IM and azithromycin 2 g orally in a single dose.
- 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 the patient to return for a TOC one week after treatment.

Please note that patients with persistent or recurrent symptoms who report interim sexual exposure to untreated or new partners most likely have been re-infected, rather than experiencing a true treatment failure. Patients likely to have been re-infected should be retreated with the recommended antibiotic regimen.

### **Implications and action steps**

Despite these multiple challenges, the updated CDC GC treatment guidelines provide an important opportunity to educate the many STD treatment providers in public and private settings regarding the ongoing threat of emerging cephalosporin resistance and the importance of using IM ceftriaxone plus oral azithromycin treatment whenever possible. Further, providers must be vigilant for treatment failures and follow current recommendations for managing and reporting suspected treatment failures. Local Health Officers have a key role in educating providers by sharing this information with clinicians and other providers in their jurisdiction.

In addition, local STD program staff should monitor GC treatment practices as reports are submitted and promote the use of IM ceftriaxone plus azithromycin during STD case management activities. 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 WDPH STD Control Section at (608) 266-7945 for assistance.

### **Links to reports**

The full CDC report is available online:

[http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s\\_cid=mm6131a3\\_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s_cid=mm6131a3_e).

Additional useful materials, including the CDC report “Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan” are also available online:

[www.cdc.gov/std/treatment](http://www.cdc.gov/std/treatment).