



Antibiotic Treatment of Gonorrhea

Concerning Laboratory Data Suggest Declining Susceptibility to Cephalosporins — Last Available Gonorrhea Treatment Option

In the July 8, 2011 issue of CDC's *Morbidity and Mortality Weekly Report*, researchers analyzed gonorrhea surveillance data and concluded that, although there have been no documented treatment failures yet, untreatable gonorrhea may become a reality in the U.S.

Gonorrhea, one of the most common sexually transmitted diseases (STDs), can have serious health consequences, including infertility in women, and can increase a person's risk for acquiring HIV. Gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. While antibiotics can successfully treat gonorrhea, over time the bacteria has developed resistance to several of these drugs, including sulfonamides, penicillin, tetracycline, and most recently, in 2007, fluoroquinolones. CDC now recommends only one class of antibiotics, called cephalosporins — consisting of the drugs cefixime (administered orally) or ceftriaxone (administered via injection) — together with another antibiotic, either azithromycin or doxycycline. However, findings from the recent analysis signal the potential for resistance to cephalosporins, the last line of defense for treating gonorrhea.

CDC officials note that individuals currently undergoing treatment for gonorrhea should continue to follow their healthcare provider's guidance. If a patient has questions or concerns about their treatment, they should contact their provider.

Trends of Declining Susceptibility to Cephalosporins

Since 1986, CDC's Gonococcal Isolate Surveillance Project (GISP) has routinely monitored gonorrhea drug susceptibility — or how *Neisseria gonorrhoeae* responds to antibiotics. The project collects *Neisseria gonorrhoeae* samples — also called isolates — from men with urethral gonorrhea at STD clinics in approximately 30 U.S. cities.

For the July 8 report, researchers analyzed susceptibility to cephalosporins among nearly 6,000 isolates each year collected through GISP between 2000 and 2010.

Researchers used two different thresholds to measure the proportion of isolates with elevated minimum inhibitory concentrations (MICs) for both available cephalosporins (for more information about MICs, see sidebar).

First, researchers considered the proportion of isolates that met a standard laboratory definition of decreased

MICs, Decreased Susceptibility, and Antibiotic Resistance

Minimum inhibitory concentrations (MICs), measured in micrograms per milliliter, are the lowest concentration of antibiotics needed to stop the bacteria's growth in the laboratory.

A strain of bacteria has *decreased susceptibility* to a given antibiotic when laboratory results indicate that higher-than-expected antibiotic concentrations are needed to stop its growth. For cefixime and ceftriaxone, the standard laboratory definition of decreased susceptibility is MICs greater than or equal to 0.5 µg/mL. Decreased susceptibility in isolates may not have any immediate clinical implications for patients.

A strain of bacteria exhibits *antibiotic resistance* when it can no longer be cured when treated with a specific antibiotic.



susceptibility — MICs greater than or equal to 0.5 µg/mL. For cefixime, only a very small number of isolates reached this threshold. And while the numbers were small, researchers observed an increase in the percentage of cases that crossed this threshold in recent years — from 0.02 percent for 2000–2006 to 0.11 percent for 2009–2010. Of note, all of the isolates with decreased susceptibility to cefixime were collected from gay or bisexual men. No isolates met the laboratory definition of decreased susceptibility to ceftriaxone during the years of the analysis.

Next, because analyzing trends with a lower threshold helps to highlight patterns in increasing MICs and declining susceptibility over time, researchers also considered trends in MICs with a lower threshold. Using this lower threshold (elevated MICs) — MICs greater than or equal to 0.25 µg/mL for cefixime, and greater than or equal to 0.125 µg/mL for ceftriaxone — researchers found:

- ▶ **Cefixime:** The proportion of samples with elevated MICs rose from 0.2 percent in 2000 to 1.4 percent in 2010.
- ▶ **Ceftriaxone:** Between 2000 and 2010, the proportion of samples with elevated MICs increased from 0.1 percent to 0.3 percent.

Patterns of elevated MICs were most prominent in samples collected in the western United States, and among gay and bisexual men:

- ▶ **Western regions:** For cefixime, the proportion of samples from the West with elevated MICs rose from zero percent in 2000 to 3.3 percent in 2010. Significant increases in the proportion of isolates with elevated MICs were noted in Hawaii (from 0 to 7.7 percent) and California (from 0 to 4.5 percent) between 2000 and 2010. Smaller, but still significant, increases were seen for ceftriaxone in the same time period in the west: the percentage of isolates with elevated MICs rose from zero to 0.5 percent.
- ▶ **Men who have sex with men (MSM):** For cefixime, the proportion of isolates with elevated MICs rose from zero to 4 percent between 2000 and 2010; for ceftriaxone, the proportion of isolates with elevated MICs rose from zero to 0.9 percent.

What Elevated MICs Tell Us

By monitoring the percentage of gonorrhea isolates that require higher doses of antibiotics to stop their growth in the lab, CDC researchers hope to gain advance warning of any future emergence of cephalosporin resistance.

Patterns Suggest Future Cephalosporin Resistance in the U.S. Likely

Currently, treatment of gonorrhea with cephalosporins does remain effective, and no cases of treatment failures have been seen in the U.S. However, the patterns of declining cephalosporin susceptibility in this analysis are reminiscent of the emergence of fluoroquinolone-resistant gonorrhea less than a decade ago. Cases of fluoroquinolone-resistant gonorrhea were initially detected in Hawaii and California (after first emerging in Asia) and became widespread among gay and bisexual men, before becoming widespread throughout the U.S.

To date, a small number of isolated cephalosporin treatment failures have been recently reported in other parts of the world, including Norway, Japan and other parts of Asia. Previous treatment failures and experience, coupled with recent findings, suggest that cephalosporin-resistant strains of gonorrhea are likely to develop in the U.S. in the coming years.



Action Needed to Address Potential for Cephalosporin-Resistant Gonorrhea

CDC is currently working with healthcare providers and state and local healthcare partners to increase gonorrhea surveillance capacity so that emerging patterns of antibiotic resistance can be recognized as they occur. CDC may modify current treatment recommendations as dictated by surveillance and susceptibility trends. However, there is an urgent need for effective new gonorrhea treatments since there are currently no well-studied and effective alternative treatments for gonorrhea.

CDC urges healthcare providers, state and local health departments, and others to take important steps to address this potential threat:

- ▶ **Healthcare Providers** — CDC encourages individual providers to:
 - Promptly treat all patients diagnosed with gonorrhea according to CDC's Treatment Guidelines; available at <http://www.cdc.gov/std/treatment/2010/>
 - Obtain cultures to test for decreased susceptibility from any patients with suspected or documented gonorrhea treatment failures
 - Report any suspected treatment failure to local or state public health officials within 24 hours, helping to ensure that any future resistance is recognized early
- ▶ **Health Departments and Laboratories** — State and local health departments and other laboratories should maintain culture capacity so that antibiotic resistance testing can be quickly performed and reported. If antibiotic resistance testing cannot be performed locally, facilities should identify and partner with other labs that can perform such testing. CDC requests health departments to develop local response plans and notify the agency of treatment failures immediately. Laboratories should also report isolates with decreased susceptibility to cefixime or ceftriaxone to local or state public health officials.
- ▶ **Public and Private Partners** — CDC urges scientists and drug development sponsors to prioritize the identification of effective new antibiotic treatments for gonorrhea. CDC is collaborating with the National Institutes of Health to test new antibiotic combinations for the bacteria. However, it is likely that many different approaches will need to be tested before suitable treatment options can be found.

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