Update to CDC's *Sexually Transmitted Diseases Treatment Guidelines, 2010*: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections

Gonorrhea is a major cause of serious reproductive complications in women and can facilitate human immunodeficiency virus (HIV) transmission (*1*). Effective treatment is a cornerstone of U.S. gonorrhea control efforts, but treatment of gonorrhea has been complicated by the ability of *Neisseria gonorrhoeae* to develop antimicrobial resistance. This report, using data from CDC's Gonococcal Isolate Surveillance Project (GISP), describes laboratory evidence of declining cefixime susceptibility among urethral *N. gonorrhoeae* isolates collected in the United States during 2006–2011 and updates CDC's current recommendations for treatment of gonorrhea (*2*). Based on GISP data, CDC recommends combination therapy with ceftriaxone 250 mg intramuscularly and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days as the most reliably effective treatment for uncomplicated gonorrhea. CDC no longer recommends cefixime at any dose as a first-line regimen for treatment of gonococcal infections. If cefixime is used as an alternative agent, then the patient should return in 1 week for a test-of-cure at the site of infection.

Infection with *N. gonorrhoeae* is a major cause of pelvic inflammatory disease, ectopic pregnancy, and infertility, and can facilitate HIV transmission (*1*). In the United States, gonorrhea is the second most commonly reported notifiable infection, with >300,000 cases reported during 2011. Gonorrhea treatment has been complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobials used for treatment. During the 1990s and 2000s, fluoroquinolone resistance in *N. gonorrhoeae* emerged in the United States, becoming prevalent in Hawaii and California and among men who have sex with men (MSM) before spreading throughout the United States. In 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted CDC to no longer recommend fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining recommended antimicrobial class (*3*). To ensure treatment of co-occurring pathogens (e.g., *Chlamydia trachomatis*) and reflecting concern about emerging gonococcal resistance, CDC's 2010 sexually transmitted diseases (STDs) treatment guidelines recommended combination therapy for gonorrhea with a cephalosporin (ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally) plus either azithromycin orally or doxycycline orally, even if nucleic acid amplification testing (NAAT) for *C. trachomatis* was negative at the time of treatment (*2*). From 2006 to 2010, the minimum concentrations of cefixime needed to inhibit the growth in vitro of *N. gonorrhoeae* strains circulating in the United States and many other countries increased, suggesting that the effectiveness of cefixime might be waning (*4*). Reports from Europe recently have described patients with uncomplicated gonorrhea infection not cured by treatment with cefixime 400 mg orally (*5*–*8*).

GISP is a CDC-supported sentinel surveillance system that has monitored *N. gonorrhoeae* antimicrobial susceptibilities since 1986, and is the only source in the United States of national and regional *N. gonorrhoeae* antimicrobial susceptibility data. During September–December 2011, CDC and five external GISP principal investigators, each with *N. gonorrhoeae*–specific expertise in surveillance, antimicrobial resistance, treatment, and antimicrobial susceptibility testing, reviewed antimicrobial susceptibility trends in GISP through August 2011 to determine whether to update CDC's current recommendations (*2*) for treatment of uncomplicated gonorrhea. Each month, the first 25 gonococcal urethral isolates collected from men attending participating STD clinics (approximately 6,000 isolates each year) were submitted for antimicrobial susceptibility testing. The minimum inhibitory concentration (MIC), the lowest antimicrobial concentration that inhibits visible bacterial growth in the laboratory, is used to assess antimicrobial susceptibility. Cefixime susceptibilities were not determined during 2007–2008 because cefixime temporarily was unavailable in the United States at that time. Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical Laboratory Standards Institute (CLSI). However, CLSI does consider isolates with cefixime or ceftriaxone MICs ≥0.5 μg/mL to have "decreased susceptibility" to these drugs (*9*). During 2006–2011, 15 (0.1%) isolates had decreased susceptibility to cefixime (all had MICs = 0.5 μg/mL), including nine (0.2%) in 2010 and one (0.03%) during January–August 2011; 12 of 15 were from MSM, and 12 were from the West and three from the Midwest.* No isolates

* U.S. Census regions. *Northeast:* Connecticut, Maine, Massachusetts, New Jersey, New Hampshire, New York, Pennsylvania, Rhode Island, and Vermont; *Midwest:* Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South:* Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; *West:* Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming.

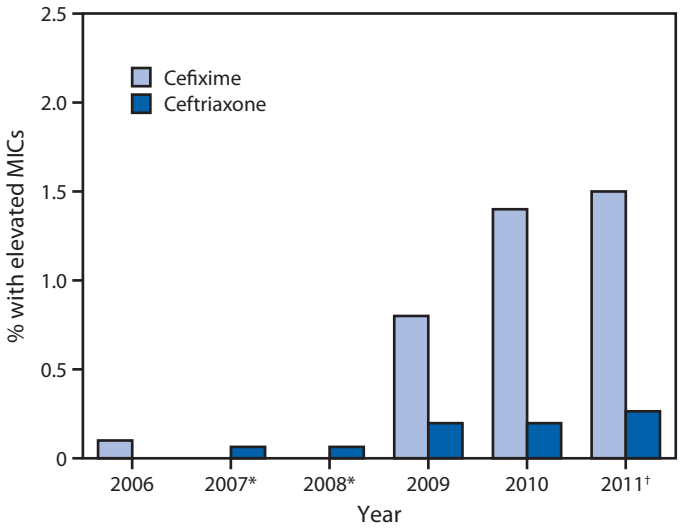
exhibited decreased susceptibility to ceftriaxone. Because increasing MICs can predict the emergence of resistance, lower cephalosporin MIC breakpoints were established by GISP for surveillance purposes to provide greater sensitivity in detecting declining gonococcal susceptibility than breakpoints defined by CLSI. Cefixime MICs ≥0.25 μg/mL and ceftriaxone MICs ≥0.125 μg/mL were defined as "elevated MICs." CLSI does not define azithromycin resistance criteria; CDC defines decreased azithromycin susceptibility as ≥2.0 μg/mL.

Evidence and Rationale

The percentage of isolates with elevated cefixime MICs (MICs ≥0.25 μg/mL) increased from 0.1% in 2006 to 1.5% during January–August 2011 (Figure). In the West, the percentage increased from 0.2% in 2006 to 3.2% in 2011 (Table). The largest increases were observed in Honolulu, Hawaii (0% in 2006 to 17.0% in 2011); Minneapolis, Minnesota (0% to 6.9%); Portland, Oregon (0% to 6.5%); and San Diego, California (0% to 6.4%). Nationally, among MSM, isolates with elevated MICs to cefixime increased from 0.2% in 2006 to 3.8% in 2011. In 2011, a higher proportion of isolates from MSM had elevated cefixime MICs than isolates from men who have sex exclusively with women (MSW), regardless of region (Table).

The percentage of isolates exhibiting elevated ceftriaxone MICs increased slightly, from 0% in 2006 to 0.4% in 2011 (Figure). The percentage increased from <0.1% in 2006 to 0.8% in 2011 in the West, and did not increase significantly in the Midwest (0% to 0.2%) or the Northeast and South (0.1% in 2006 and 2011). Among MSM, the percentage increased from 0.0% in 2006 to 1.0% in 2011.

FIGURE. Percentage of urethral *Neisseria gonorrhoeae* isolates (n = 32,794) with elevated cefixime MICs (≥0.25 μg/mL) and ceftriaxone MICs (≥0.125 μg/mL) — Gonococcal Isolate Surveillance Project, United States, 2006–August 2011



Abbreviation: MICs = minimum inhibitory concentrations.
* Cefixime susceptibility not tested during 2007–2008.
† January–August 2011.

The 2010 CDC STD treatment guidelines (*2*) recommend that azithromycin or doxycycline be administered with a cephalosporin as treatment for gonorrhea. The percentage of isolates exhibiting tetracycline resistance (MIC ≥2.0 μg/mL) was high but remained stable from 2006 (20.6%) to 2011 (21.6%). The percentage exhibiting decreased susceptibility to azithromycin (MIC ≥2.0 μg/mL) remained low (0.2% in 2006 to 0.3% in 2011). Among 180 isolates collected during 2006–2011 that exhibited elevated cefixime MICs, 139 (77.2%) exhibited

TABLE. Percentage of urethral *Neisseria gonorrhoeae* isolates with elevated cefixime MICs (≥0.25 μg/mL), by U.S. Census region and gender of sex partner — Gonococcal Isolate Surveillance Project, United States, 2006–August 2011

	2006		2009		2010		2011*	
Region	**%**	**(95% CI)**	**%**	**(95% CI)**	**%**	**(95% CI)**	**%**	**(95% CI)**
West† (total)	**0.2**	**(0.1–0.4)**	**1.9**	**(1.4–2.6)**	**3.3**	**(2.6–4.0)**	**3.2**	**(2.3–4.2)**
MSM	0.1	(0.0–0.6)	2.6	(1.7–3.8)	5.0	(3.8–6.5)	4.5	(3.1–6.3)
MSW	0.2	(0.0–0.6)	1.4	(0.7–2.3)	1.3	(0.7–2.2)	1.8	(0.9–3.1)
Midwest§ (total)	**0.0**	**(0.0–0.3)**	**0.5**	**(0.2–1.0)**	**0.5**	**(0.2–1.1)**	**0.6**	**(0.2–1.5)**
MSM	0.0	(0.0–2.8)	2.3	(0.6–5.7)	3.4	(1.1–7.7)	4.9	(1.4–12.2)
MSW	0.0	(0.0–0.3)	0.3	(0.1–0.7)	0.1	(0.0–0.6)	0.0	(0.0–0.6)
Northeast and South¶ (total)	**0.1**	**(0.0–0.3)**	**0.0**	**(0.0–0.2)**	**0.1**	**(0.0–0.4)**	**0.3**	**(0.1–0.8)**
MSM	0.6	(0.0–3.0)	0.3	(0.0–1.9)	0.9	(0.2–2.5)	1.5	(0.4–3.9)
MSW	0.0	(0.0–0.2)	0.0	(0.0–0.2)	0.0	(0.0–0.2)	0.1	(0.0–0.4)

Abbreviations: CI = confidence interval; MICs = minimum inhibitory concentrations; MSM = men who have sex with men; MSW = men who have sex exclusively with women.
* January–August 2011.
† Includes data from Albuquerque, New Mexico; Denver, Colorado; Honolulu, Hawaii; Las Vegas, Nevada; Los Angeles, California; Orange County, California; Phoenix, Arizona; Portland, Oregon; San Diego, California; San Francisco, California; and Seattle, Washington.
§ Includes data from Chicago, Illinois; Cincinnati, Ohio; Cleveland, Ohio; Detroit, Michigan; Kansas City, Missouri; and Minneapolis, Minnesota.
¶ Includes data from Atlanta, Georgia; Baltimore, Maryland; Birmingham, Alabama; Dallas, Texas; Greensboro, North Carolina; Miami, Florida; New Orleans, Louisiana; New York, New York; Oklahoma City, Oklahoma; Philadelphia, Pennsylvania; and Richmond, Virginia.

tetracycline resistance, but only one (0.6%) had decreased susceptibility to azithromycin.

Ceftriaxone as a single intramuscular injection of 250 mg provides high and sustained bactericidal levels in the blood and is highly efficacious at all anatomic sites of infection for treatment of *N. gonorrhoeae* infections caused by strains currently circulating in the United States (*10,11*). Clinical data to support use of doses of ceftriaxone >250 mg are not available. A 400-mg oral dose of cefixime does not provide bactericidal levels as high, nor as sustained as does an intramuscular 250-mg dose of ceftriaxone, and demonstrates limited efficacy for treatment of pharyngeal gonorrhea (*10,11*). The significant increase in the prevalence of U.S. GISP isolates with elevated cefixime MICs, most notably in the West and among MSM, is of particular concern because the emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States during the 1990s also occurred initially in the West and predominantly among MSM before spreading throughout the United States within several years. Thus, observed patterns might indicate early stages of the development of clinically significant gonococcal resistance to cephalosporins. CDC anticipates that rising cefixime MICs soon will result in declining effectiveness of cefixime for the treatment of urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued use of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last antimicrobial that is recommended and known to be highly effective in a single dose for treatment of gonorrhea at all anatomic sites of infection. Maintaining effectiveness of ceftriaxone for as long as possible is critical. Thus, CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States.

Based on experience with other microbes that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using two antimicrobials with different mechanisms of action to improve treatment efficacy and potentially delay emergence and spread of resistance to cephalosporins. Therefore, the use of a second antimicrobial (azithromycin as a single 1-g oral dose or doxycycline 100 mg orally twice daily for 7 days) is recommended for administration with ceftriaxone. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among GISP isolates, particularly in strains with elevated cefixime MICs.

Recommendations

For treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, CDC recommends combination therapy with a single intramuscular dose of ceftriaxone 250 mg plus either a single dose of azithromycin 1 g orally or doxycycline 100 mg orally twice daily for 7 days (Box).

Clinicians who diagnose gonorrhea in a patient with persistent infection after treatment (treatment failure) with the recommended combination therapy regimen should culture relevant clinical specimens and perform antimicrobial susceptibility testing of *N. gonorrhoeae* isolates. Phenotypic antimicrobial susceptibility testing should be performed using disk diffusion, Etest (BioMérieux, Durham, NC), or agar dilution. Data currently are limited on the use of NAAT-based antimicrobial susceptibility testing for genetic mutations associated with

BOX. Updated recommended treatment regimens for gonococcal infections

Uncomplicated gonococcal infections of the cervix, urethra, and rectum

Recommended regimen

Ceftriaxone 250 mg in a single intramuscular dose
PLUS
Azithromycin 1 g orally in a single dose
or doxycycline 100 mg orally twice daily for 7 days*

Alternative regimens

If ceftriaxone is not available:
Cefixime 400 mg in a single oral dose
PLUS
Azithromycin 1 g orally in a single dose
or doxycycline 100 mg orally twice daily for 7 days*
PLUS
Test-of-cure in 1 week

If the patient has severe cephalosporin allergy:
Azithromycin 2 g in a single oral dose
PLUS
Test-of-cure in 1 week

Uncomplicated gonococcal infections of the pharynx

Recommended regimen

Ceftriaxone 250 mg in a single intramuscular dose
PLUS
Azithromycin 1 g orally in a single dose
or doxycycline 100 mg orally twice daily for 7 days*

*Because of the high prevalence of tetracycline resistance among Gonococcal Isolate Surveillance Project isolates, particularly those with elevated minimum inhibitory concentrations to cefixime, the use of azithromycin as the second antimicrobial is preferred.

resistance in *N. gonorrhoeae*. The laboratory should retain the isolate for possible further testing. The treating clinician should consult an infectious disease specialist, an STD/HIV Prevention Training Center (http://www.nnptc.org), or CDC (telephone: 404-639-8659) for treatment advice, and report the case to CDC through the local or state health department within 24 hours of diagnosis. A test-of-cure should be conducted 1 week after re-treatment, and clinicians should ensure that the patient's sex partners from the preceding 60 days are evaluated promptly with culture and treated as indicated.

When ceftriaxone cannot be used for treatment of urogenital or rectal gonorrhea, two alternative options are available: cefixime 400 mg orally plus either azithromycin 1 g orally or doxycycline 100 mg twice daily orally for 7 days if ceftriaxone is not readily available, or azithromycin 2 g orally in a single dose if ceftriaxone cannot be given because of severe allergy. If a patient with gonorrhea is treated with an alternative regimen, the patient should return 1 week after treatment for a test-of-cure at the infected anatomic site. The test-of-cure ideally should be performed with culture or with a NAAT for *N. gonorrhoeae* if culture is not readily available. If the NAAT is positive, every effort should be made to perform a confirmatory culture. All positive cultures for test-of-cure should undergo phenotypic antimicrobial susceptibility testing. Patients who experience treatment failure after treatment with alternative regimens should be treated with ceftriaxone 250 mg as a single intramuscular dose and azithromycin 2 g orally as a single dose and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.

For all patients with gonorrhea, every effort should be made to ensure that the patients' sex partners from the preceding 60 days are evaluated and treated for *N. gonorrhoeae* with a recommended regimen. If a heterosexual partner of a patient cannot be linked to evaluation and treatment in a timely fashion, then expedited partner therapy should be considered, using oral combination antimicrobial therapy for gonorrhea (cefixime 400 mg and azithromycin 1 g) delivered to the partner by the patient, a disease investigation specialist, or through a collaborating pharmacy.

The capacity of laboratories in the United States to isolate *N. gonorrhoeae* by culture is declining rapidly because of the widespread use of NAATs for gonorrhea diagnosis, yet it is essential that culture capacity for *N. gonorrhoeae* be maintained to monitor antimicrobial resistance trends and determine susceptibility to guide treatment following treatment failure. To help control gonorrhea in the United States, health-care providers must maintain the ability to collect specimens for culture and be knowledgeable of laboratories to which they can send specimens for culture. Health-care systems and health departments must support access to culture, and laboratories must maintain culture capacity or develop partnerships with laboratories that can perform culture.

Treatment of patients with gonorrhea with the most effective therapy will limit the transmission of gonorrhea, prevent complications, and likely will slow emergence of resistance. However, resistance to cephalosporins, including ceftriaxone, is expected to emerge. Reinvestment in gonorrhea prevention and control is warranted. New treatment options for gonorrhea are urgently needed.

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