

*epi*TRENDS

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The Growing Threat of Cephalosporin-Resistant *Neisseria gonorrhoeae*

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Infection with *Neisseria gonorrhoeae* is the second most common notifiable condition in the country, following chlamydia. Treatment regimens for gonorrhea have changed frequently over the past few decades due to the organism's propensity for developing antibiotic resistance. Over the past few years, *N. gonorrhoeae* have become less susceptible to the third generation cephalosporins. This trend is concerning because no alternative antibiotic treatment options or combinations have been proven to be effective against the organism.

The Disease

In 1879 Albert Neisser discovered the gonococcus which was later demonstrated as the etiologic agent of gonorrhea. Gonorrhea is a sexually transmitted bacterial infection that primarily affects the reproductive tract



Neisseria gonorrhoeae within a white cell (CDC)

but can also affect the rectum, throat, or eyes. The infection may be asymptomatic, particularly in women. Typical symptoms due to inflammation of the mucosa with purulent discharge were recognized by early healthcare providers including Galen, who named the condition from Greek roots meaning flow (rheo) of seed (gonos). Complications include pelvic inflammatory disease with increased risk for ectopic pregnancy or infertility, and occasional infections of the liver, skin, joints, and rarely meninges. Antibiotic treatment of eyes at birth is widely mandated to prevent infant blindness from gonorrheal ophthalmia neonatorum.

The first effective treatment for gonorrhea was sulfonilamide antibiotics introduced in 1937. Rapidly developed resistance soon necessitated increasing doses. Penicillin became a treatment option in 1943 with

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resistant cases first reported in 1946, again requiring increased antibiotic doses. Probenecid was added to penicillin in the 1970s to counter resistance, but by 1989 other antibiotics became the preferred treatment. By 1993, cephalosporins and fluoroquinolones replaced tetracycline and erythromycin as recommended gonorrhea treatment options. Fluoroquinolones were no longer recommended as of 2007 because resistance to this class of antibiotics had emerged. Since then, cephalosporins have been the antibiotics of choice.

Growing Threat of Cephalosporin Resistance

The Gonococcal Isolate Surveillance Project (GISP) is a national sentinel surveillance system established in the 1980s to monitor antimicrobial resistance in *N. gonorrhoeae*. As part of this project, 25-30 participating clinics across the United States submit *N. gonorrhoeae* isolates from men to five regional laboratories, including a laboratory in Seattle, for susceptibility testing to penicillin, tetracycline, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, and azithromycin. GISP data are used to guide national treatment recommendations and are available on the Centers for Disease Control and Prevention (CDC) web site at: <http://www.cdc.gov/std/gisp2010/default.htm>

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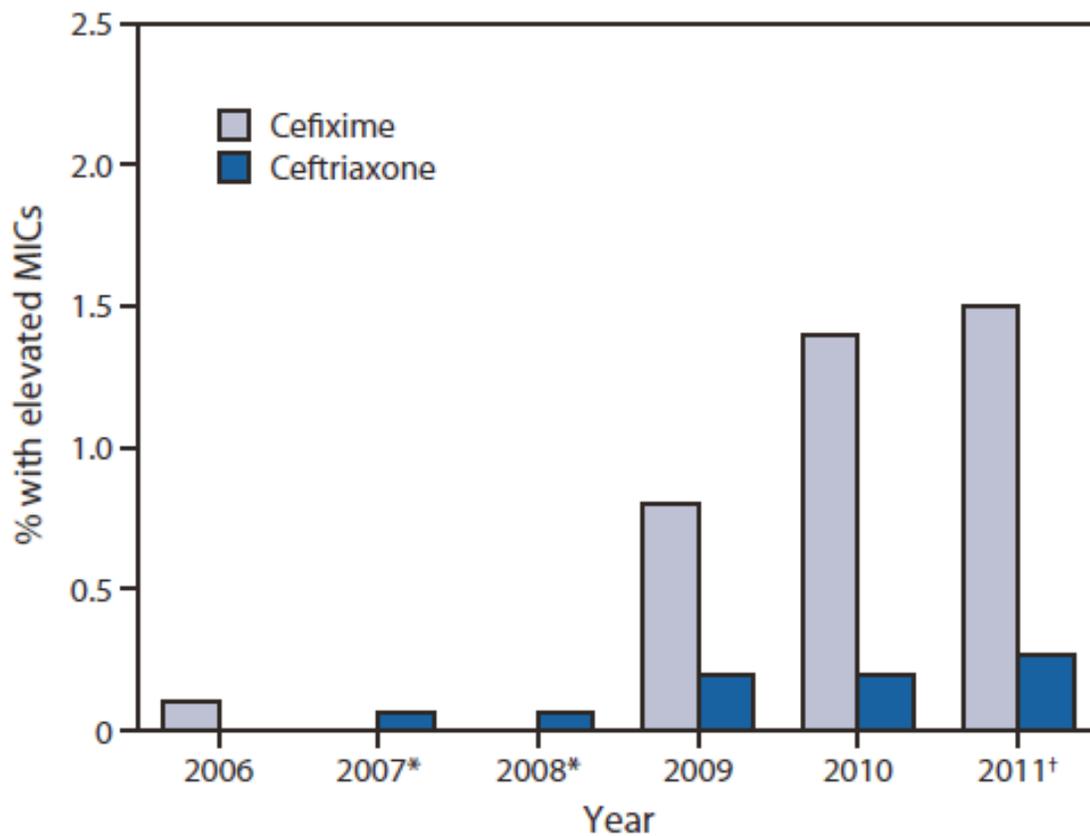


Penicillin poster, 1944, National Library of Medicine

During 2006–2011, GISP detected 15 (0.1%) *N. gonorrhoeae* isolates with “decreased susceptibility” to cefixime and no isolates with decreased susceptibility to ceftriaxone (defined as a minimum inhibitory concentration [MIC] $\geq 0.5 \mu\text{g/mL}$). However, recent GISP data are showing an increasing proportion of isolates with “elevated MICs” (defined as $\geq 0.25 \mu\text{g/mL}$ for cefixime and $\geq 0.125 \mu\text{g/mL}$ for ceftriaxone) which suggests that susceptibility to cephalosporins might be decreasing. Overall, the proportion of isolates with elevated MICs

for cefixime increased 15-fold from 0.1% in 2006 to 1.5% in 2011 while the proportion of isolates with elevated MICs for ceftriaxone increased slightly from 0% in 2006 to 0.4% in 2011 (Figure). Gonococcal isolates collected in western states (including Seattle) and from men having sex with men are more likely to have elevated MICs compared to those collected in other parts of the country and to those collected from men having sex exclusively with women. Isolates from Portland, Oregon, had among the largest increases, with 6.5% of cefixime isolates having elevated MICs in 2011. These trends are concerning because they parallel trends seen during the development of fluoroquinolone resistance.

FIGURE . Percentage of urethral *Neisseria gonorrhoeae* isolates (n = 32,794) with elevated cefixime MICs ($\geq 0.25 \mu\text{g/mL}$) and ceftriaxone MICs ($\geq 0.125 \mu\text{g/mL}$) — Gonococcal Isolate Surveillance Project, United States, 2006–August 2011



Abbreviation: MICs = minimum inhibitory concentrations.

* Cefixime susceptibility not tested during 2007–2008.

† January–August 2011.

Decreased susceptibility to cephalosporins has been reported recently in Asia and several European countries. In 2009, a patient from Japan was found to be infected with a strain of *N.*

gonorrhoeae that was highly resistant to cephalosporins. Treatment failures with oral cefixime have been reported from Europe.

Recommendations

Currently, CDC recommends dual therapy with ceftriaxone 250 mg in a single intramuscular dose and either azithromycin 1 gram in a single oral dose or doxycycline 100 mg orally twice daily for 7 days for treatment of uncomplicated gonococcal infections in adolescents and adults. A second antibiotic (azithromycin or doxycycline) is included to treat *C. trachomatis*, a common co-infection, and potentially reduce the emergence of cephalosporin resistance. Azithromycin is preferred over doxycycline because it is a single dose and strains with decreased susceptibility to cefixime have also been shown to have decreased susceptibility to tetracyclines. As of August 9, 2012, CDC no longer recommends cefixime as a first line treatment for gonorrhea. If cefixime or other alternative therapy is used, CDC recommends that a test-of-cure is performed one week after treatment, preferably using culture. If culture is not available use nucleic acid amplification testing (NAAT).

Although increasingly used for diagnosis, non-culture-based laboratory methods such as nucleic acid amplification tests (NAAT) cannot be used for antibiotic susceptibility testing. Therefore, if a patient fails to respond to therapy, the providers should perform a culture, request susceptibility testing if *N. gonorrhoeae* is isolated, and report the patient to their local health department. The provider should also perform a test of cure one week after re-treatment.

Sexual partners during the prior 60 days of those with gonorrhea should be referred for evaluation and treated with a recommended antibiotic regimen. Expedited Partner Therapy (EPT) can be used for heterosexual partners if a patient cannot be linked to screening and treatment.

If *N. gonorrhoeae* develops resistance to third generation cephalosporins, there will be few therapeutic options remaining. Potential measures would be increased antibiotic dosages or using new combination therapies. Research could provide new antibiotics and even a vaccine against gonorrhea. Public health prevention measures to reduce the burden of gonorrhea include clinical referral services, partner services, and interventions among populations at high risk for sexually transmitted infections. Appropriate antibiotic treatment and follow-up of all gonorrhea cases is essential for retaining the available therapeutic options.

Link: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm?s_cid=mm6131a3_e