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Perspective

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The Emerging Threat of Untreatable Gonococcal Infection

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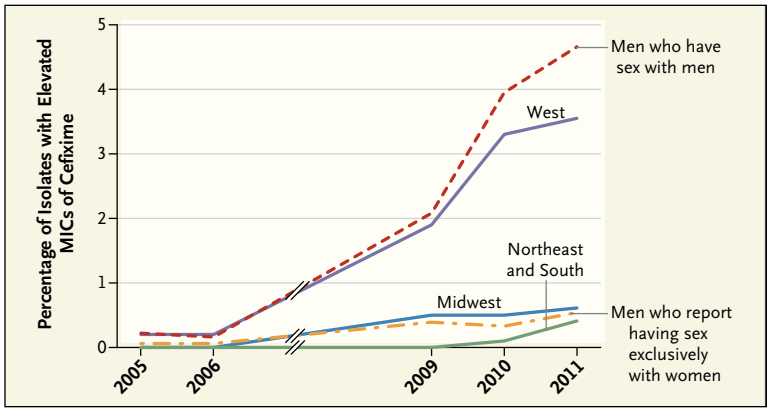
It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense, threatening our ability to cure gonorrhea and prevent severe sequelae.

Gonorrhea is the second most commonly reported communicable disease in the United States, with an estimated incidence of more than 600,000 cases annually. It disproportionately affects vulnerable populations such as minorities who are marginalized because of race, ethnic group, or sexual orientation. Unfortunately, *Neisseria gonorrhoeae* has always readily developed resistance to antimicrobial agents: it became resistant to sulfanilamide in the 1940s, penicillins and tetracyclines in the 1980s, and fluoroquinolones by 2007.[1] When the prevalence of antimicrobial resistance in the Gonococcal Isolate Surveillance Project (GISP) exceeds 5%, national treatment recommendations are changed to focus on other effective drugs. However, the treatment options recommended by the Centers for Disease Control and Prevention (CDC) are now limited to third-generation cephalosporins.[2]

But susceptibility to cephalosporins has been decreasing rapidly.[3] The proportion of GISP isolates for which the minimum inhibitory concentration (MIC) of cefixime is elevated (≥0.25 μg per milliliter) has increased by a factor of 17 — from 0.1% in 2006 to 1.7% in the first 6 months of 2011. (Although the MIC breakpoints for resistance to cephalosporin have not been defined, the Clinical and Laboratory Standards Institute defines susceptibility to cefixime and ceftriaxone as MICs of 0.25 μg per milliliter or below.) The increases were most pronounced in the western United States (from 0.2% to 3.6%) and among men who have sex with men (from 0.2% to 4.7%) (see graph). Although only one isolate (0.04% of those in the GISP) had a MIC of ceftriaxone of 0.25 μg per milliliter in the first half of 2011, the proportion of GISP isolates with an elevated ceftriaxone MIC (≥0.125 μg per milliliter) has increased by a factor of 10 since 2006 (from 0.05% to 0.50%). Again, increases were greatest in the west (from 0.04% to 1.90%) and among men who have sex with men (from 0.0% to 1.0%). These geographic and demographic patterns are worrisome because they mirror those observed during the emergence of fluoroquinolone-resistant *N. gonorrhoeae*.

Reduced susceptibility to cephalosporins results from the combined effects of several chromosomal gene mutations, including mutations in *penA*, the gene that encodes penicillin-binding protein 2 (PBP2); *penB*, which affects drug entry through an outer membrane protein channel (PorB1b), and *mtrR*, a repressor of the MtrCDE-encoded pump. A novel DNA cassette with multiple *penA* mutations (mosaic *penA*) is common in strains with reduced sus-



Percentage of Isolates in Which Minimal Inhibitory Concentrations (MICs) of Cefixime Were 0.25 μg per Milliliter or Higher, 2005–2011.

Susceptibility to cefixime was not tested in 2007 or 2008. From the Gonococcal Isolate Surveillance Project.

ceptibility to cefixime; the cassette may have been acquired through horizontal transfer from oral commensal neisseria.

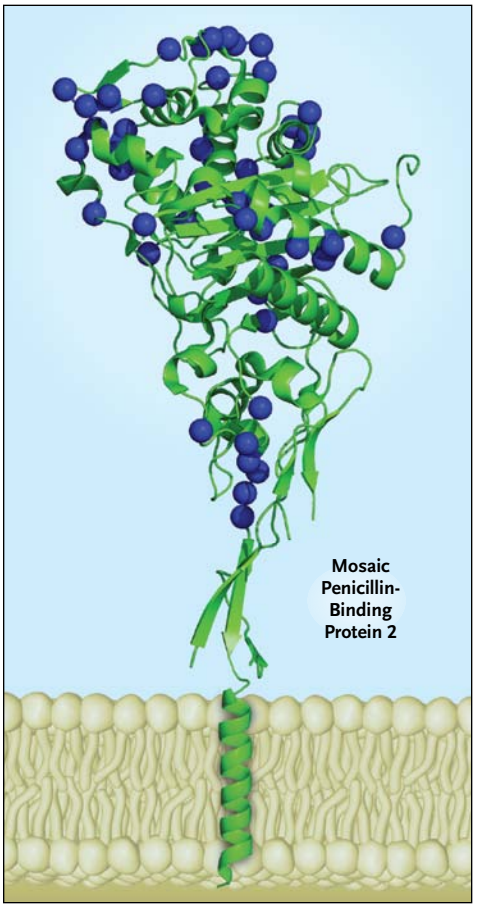
Decreased susceptibility to cefixime was first reported in East Asia, and possible failure of treatment with cefixime was noted in Japan in 2003 and was later documented in Norway and the United Kingdom in 2010. The greatest worry is the strain isolated in Kyoto in 2009 from a patient with pharyngeal gonorrhea that was highly resistant to ceftriaxone (with MICs of 2.0 to 4.0 μg per milliliter). This strain is related to earlier clones with reduced cefixime susceptibility, but it carries a different version of the *penA* mosaic gene.[4] It has been almost 3 years since it was detected in Japan, so it may not be highly pathogenic. If history is any guide, however, such strains will continue to evolve. Indeed, we should anticipate the emergence of fit cephalosporin-resistant strains that can spread widely.

It is not known whether higher doses of cephalosporins can mitigate the threat of the emergence of ceftriaxone-resistant strains. Although third-generation cephalosporins are still highly effective against most U.S. gonorrhea strains, investing in rebuilding our defenses against gonococcal infections now, with involvement of the health care, public health, and research communities, is paramount if we are to control the spread and reduce the consequences of cephalosporin-resistant strains.

The first priority for clinicians is to treat all cases of gonorrhea with the most effective regimen. A 250-mg intramuscular dose of ceftriaxone is most effective in curing gonococcal infections at both genital and extragenital sites. One gram of azithromycin should also be given orally to cover other copathogens and to provide another antimicrobial with activity against *N. gonorrhoeae* at a different molecular target. Doxycycline seems less preferable, since gonococcal strains with decreased susceptibility to cefixime currently exhibit tetracycline resistance as well.[3] Oral cefixime should be reserved for situations that preclude ceftriaxone treatment. In patients who are allergic to cephalosporins, the only option is 2 g of azithromycin orally. However, 126 GISP isolates with reduced susceptibility to azithromycin (at MIC ≥2 μg per milliliter) have been reported in the United States since 2005, including 27 (0.5% of GISP isolates) in 2010, and the first strain with high-level resistance to azithromycin (MIC ≥512 μg per milliliter) identified in the United States was detected in Hawaii in 2011.[5]

All patients treated for gonorrhea should routinely be offered condoms, referred for risk-reduction counseling, and retested for gonorrhea 3 months later.[2] Sex partners with whom the patient has had contact in the previous 2 months should be treated with ceftriaxone and azithromycin. Gonorrhea treatment does not differ for persons who are infected with the human immunodeficiency virus (HIV), but gonorrhea is a risk marker for HIV infection. All patients with gonorrhea should be tested for HIV, and those who test negative should be retested 3 to 6 months later.

The second priority is to be vigilant for cases in which cephalosporin treatment has failed. In terms of laboratory capacity for the detection of *N. gonorrhoeae*, the shift from culture-based methods, which are necessary for antimicrobial-susceptibility testing, to nucleic acid–amplification tests, which cannot currently detect the genetic markers of cephalosporin-resistant gonorrhea, makes it more difficult to identify treatment failures. Patients who return with persistent or recurrent symptoms shortly after treatment should be retested for gonorrhea by culture, and isolates should be submitted for antimicrobial-susceptibility testing. Clinicians caring for men who have sex with men, especially on the West Coast or in Hawaii, should consider performing a test of cure with a culture or a nucleic acid–amplification test 1 week after treatment, particularly if cefixime is administered. Any case of



Courtesy of Rob Nicholas, University of North Carolina.

Mechanisms of Reduced Susceptibility to Cephalosporins in *N. gonorrhoeae*.

Mutations (blue dots) in the penA gene decrease inactivation of penicillin-binding protein 2, the primary mechanism underlying reduced susceptibility.

suspected treatment failure or a positive result after gonorrhea treatment should be reported promptly to local or state health departments, according to local regulations.

The local and regional laboratory capacity for gonococcal culture and antimicrobial-susceptibility testing must be rebuilt, and clinicians need protocols for the transporting of culture specimens to laboratories, as well as information about which laboratories have the capacity to perform gonococcal culture testing. Health plans that restrict coverage to only one type of test per visit should instead allow reimbursement for both gonococcal nucleic acid–amplification tests and cultures when patients are being evaluated for reinfection or cure. The GISP is a national sentinel surveillance system designed to monitor trends in MICs and to inform treatment recommendations. Yet GISP samples less than 2% of all reported gonorrhea cases and cannot provide results quickly enough. A surveillance infrastructure for resistant gonorrhea must be implemented at the local level to be more timely and effective.

For the long term, a gonococcal vaccine remains key to prevention and control, but that is a distant goal. The immediate priority is replenishing the drug pipeline to treat gonococcal infections. Only one clinical trial, sponsored by the National Institute of Allergy and Infectious Diseases, is under way to examine therapeutic options for gonorrhea involving novel combinations of existing drugs. Improved transport media are needed for patients who are evaluated in settings that lack on-site laboratories with culture capacity. The development of molecular tests for detecting an expanded spectrum of antimicrobial resistance would facilitate both clinical management and monitoring of resistance trends.

There is much to do, and the threat of untreatable gonorrhea is emerging rapidly.

The views expressed in this article are those of the authors and do not necessarily represent those of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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All Heat, No Light — The States' Medicaid Claims before the Supreme Court

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It has been clear for some time that the political fight over the minimum-insurance-coverage requirement in the Affordable Care Act (ACA) would eventually reach the U.S. Supreme Court. What few would have predicted was that the question of the constitutionality of the latest in a long line of Medicaid expansions would also end up there.

In their appeal to the Supreme