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. 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.

But susceptibility to cephalosporins has been decreasing rapidly. 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-
Susceptibility to cefixime was not tested in 2007 or 2008. From the Gonococcal Isolate Surveillance Project.

Susceptibility to cefixime; the casette 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. 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 an antibiotic-susceptibility testing, to nucleic acid–amplification tests, 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
The threat of untreatable gonococcal infection 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 Court, the plaintiffs are asking the court to strike down provisions of the ACA that would have phased in expanded Medicaid coverage over the next decade. The states argue that the Medicaid expansions would impose an unconstitutional financial burden on the states, which would be forced to spend money on health care for low-income adults without an adequate federal matching fund.

The states’ Medicaid claims are part of a broader political fight over the constitutionality of the ACA. The plaintiffs in the case argue that the provisions of the ACA that mandate health insurance coverage for all Americans and expand Medicaid are unconstitutional because they exceed Congress’s enumerated powers under the Constitution.

The plaintiffs in the case argue that the provisions of the ACA that mandate health insurance coverage for all Americans and expand Medicaid are unconstitutional because they exceed Congress’s enumerated powers under the Constitution. The plaintiffs argue that the Constitution does not authorize Congress to mandate health insurance coverage for all Americans, and that Congress cannot constitutionally expand Medicaid without a federal matching fund.

The Supreme Court will hear oral arguments in the case on March 27, 2012. The Court will then issue a decision in the case, which is expected to be announced in late June or early July. The decision will have far-reaching implications for the future of health care policy in the United States.