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-
The threat of untreatable gonococcal infection

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

It is not known whether higher doses of cefalosporins 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 cefalosporin-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 antibiotic coverage 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 resistance to azithromycin (MIC ≥512 µg per milliliter) identified in the United States was detected in Hawaii in 2011.5

Al 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 cefalosporin 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 cefalosporin-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 drug resistance that appears in our defenses against gonococcal infections, we may have to begin considering other classes of medicines.
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.

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

Sara Rosenbaum, J.D., and Timothy Stoltzfus Jost, J.D.

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...