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EDITORIAL

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Cephalosporin-Resistant Gonorrhea in North America

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GONORRHEA HAS AFFECTED HUMANS FOR CENTURIES and remains common. Worldwide, an estimated 106.1 million cases occur annually.[1] In 2011, gonorrhea again was the second most commonly reported notifiable infection in the United States with 321 849 cases reported.[2] Because gonorrhea often can be asymptomatic, the true disease burden may be closer to 700 000.[3] Gonorrhea disproportionately affects racial, ethnic, and sexual minorities. Untreated gonococcal infection can lead to pelvic inflammatory disease, ectopic pregnancy, and infertility in women and can facilitate transmission of human immunodeficiency virus.[4] Childhood blindness still affects infants born to mothers infected with gonorrhea, particularly in resource-limited countries.

For years, gonorrhea has been easily treated with a single oral dose of antibiotics. However, *Neisseria gonorrhoeae* has progressively acquired resistance to each new agent: sulfonamides in the 1940s, penicillins and tetracyclines in the 1970s and 1980s, and fluoroquinolones by 2007 in the United States. Since then, cephalosporins have been the only antibiotics recommended for gonorrhea treatment.[5] However, gonococcal susceptibility to oral cephalosporins is declining, and the effectiveness of these drugs is threatened.

Increasing cephalosporin minimum inhibitory concentrations (MICs), an early warning of impending resistance, and treatment failures with cephalosporins have been reported from east Asia since the early 2000s and recently have been reported from Europe.[6,7] In the United States, the Gonococcal Isolate Surveillance Project (GISP), a national surveillance system that monitors trends in antibiotic susceptibility, has documented increasing cefixime MICs since 2009.[8] The steepest cefixime MIC increases have been reported in the western United States and among individuals who have had male-to-male sexual contact, the region and population in which fluoroquinolone resistance initially emerged. However, data are lacking on the cefixime MICs at which clinical effectiveness wanes.

See also p 163.

In this issue of *JAMA*, Allen and colleagues[9] report a retrospective cohort study conducted to determine the risk of gonorrhea treatment failure associated with *N gonorrhoeae* strains exhibiting reduced cefixime susceptibility (defined by the authors as MIC ≥0.12 μg/mL). The authors used data from an Ontario clinic that routinely obtained cultures from patients with gonorrhea; treated them with cefixime, 400 mg, orally; and requested test of cure 2 to 4 weeks after treatment. Patients were considered to have experienced treatment failure if, at follow-up, they were culture-positive with a gonococcal isolate that was identical to the pretreatment isolate by molecular characterization and they denied sexual reexposure. Of 291 patients with positive cultures for *N gonorrhoeae*, 133 (46%) returned for tests of cure, 9 (6.8%) of whom met the case definition for treatment failure. Among the 28 patients whose pretreatment isolates demonstrated cefixime MICs 0.12 μg/mL or greater, 25% failed treatment. To account for possible bias, the authors also calculated treatment failure rate assuming that those who did not return were successfully treated; in this analysis, the treatment failure rate among patients whose pretreatment isolates demonstrated reduced cefixime susceptibility was 11.9% (7/59).

Several caveats should be noted in interpreting these results. At least some of the patients who met the treatment failure case definition may have been reinfected. The treatment failure case definition relied on medical record documentation that a patient was not reexposed and molecular techniques to determine that pretreatment and posttreatment isolates were identical. Social desirability bias, stigma, or shame could contribute to inaccurate reporting of interim sexual activity. Furthermore, although pretreatment and posttreatment isolates were identical by molecular techniques, patients reinfected from an untreated partner would be expected to be reinfected with the same strain.

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Some clinicians may be surprised that cefixime MICs less than 0.03 to 0.12 μg/mL could be associated with treatment failure. However, lack of standardization of agar dilution antimicrobial susceptibility testing techniques across laboratories complicates interpretation of MIC results. Despite these caveats, the data presented and genetic similarities between the treatment failure strains from Toronto and strains collected previously from patients whose treatment failed in Europe strongly suggest that the report by Allen et al describes the first case series of gonococcal cephalosporin treatment failure identified in North America.

When studied in the 1980s and 1990s, cefixime exhibited efficacy of 96.0% to 100.0% for urogenital gonorrhea.[10] Oral cefixime has been useful in settings in which injectable therapy is not feasible and for expedited partner therapy to prevent reinfection by providing gonorrhea treatment to unexamined sexual partners who are unlikely to seek care. However, as gonococcal cefixime MICs increase, cefixime effectiveness is threatened. The United Kingdom, Europe, and the United States have recently updated gonorrhea treatment guidelines and now list cefixime as a second-line drug to be used only when ceftriaxone is not available.[8,11,12]

On August 10, 2012, the Centers for Disease Control and Prevention (CDC) released updated gonorrhea treatment recommendations that list only dual therapy with ceftriaxone, 250 mg, and either azithromycin or doxycycline as first-line therapy.[8] Dual therapy with cefixime and either azithromycin or doxycycline is considered second-line, and its use should be followed by a test of cure. This change was based on increasing prevalence of isolates with elevated cefixime MICs (≥0.25 μg/mL) observed in the GISP. It provides an impetus for clinical settings that currently lack ceftriaxone to ensure that the antibiotic is available for treatment of gonorrhea. The Canadian guidelines still include cefixime as a recommended option but at an 800-mg dose.[13] Pharmacokinetic modeling suggests only a marginal benefit from increasing the dose to 800 mg, and even that benefit could be lost as MICs increase.[14]

In the United States, widespread use of nucleic acid amplification tests has contributed to a substantial decline in *N gonorrhoeae* culture capacity. Because gonococcal isolates from culture are necessary for antimicrobial susceptibility testing, this decline has greatly limited clinicians' ability to detect resistant infections. Although culture is no longer a primary diagnostic test, it must be readily available for quality care.

Over the past decade, *N gonorrhoeae* strains with reduced cephalosporin susceptibility have been documented across the globe. Allen et al report that cephalosporin treatment failures have now been documented in North America. Although this milestone was expected, its arrival is deeply troubling; clinicians now face the emergence of cephalosporin-resistant *N gonorrhoeae* without any well-studied, effective backup treatment options.

Gonorrhea control in the United States relies on early identification and treatment, and therefore, clinicians must be at the forefront of the response to the arrival of cephalosporin-resistant gonorrhea in North America. Clinicians should treat patients diagnosed with gonorrhea with the highly effective, CDC-recommended regimen: ceftriaxone, 250 mg, as a single intramuscular dose plus either azithromycin, 1 g, or doxycycline, 100 mg, orally twice daily for a week.[8] Because tetracycline resistance is common, azithromycin is preferred over doxycycline for gonorrhea treatment. Cefixime should only be prescribed if ceftriaxone is not available and should be followed by a test of cure. Pharyngeal gonorrhea must be treated with ceftriaxone; cefixime does not reliably eradicate this infection. All patients treated for gonorrhea should be given risk reduction counseling, offered condoms, and retested for gonorrhea 3 months after treatment.

Clinicians must make every effort to ensure that all partners with whom the patient had sexual contact within the previous 2 months are treated with ceftriaxone plus azithromycin or doxycycline. If a heterosexual partner cannot access care quickly, then expedited partner therapy with cefixime and azithromycin can be considered.

Clinicians must remain vigilant for cephalosporin treatment failures and report suspected cases to the local or state health department. Patients with persistent or recurrent symptoms shortly after treatment should be retested for gonorrhea by culture and isolates tested for antimicrobial susceptibility.[15] Clinicians must know which laboratories perform *N gonorrhoeae* culture and susceptibility testing. To support clinicians, laboratory culture and antimicrobial susceptibility testing capacity must be rebuilt.[16]

New antibiotics for treating gonococcal infections are needed. A clinical trial sponsored by the National Institute of Allergy and Infectious Diseases examining novel combinations of existing drugs (NCT00926796) just completed enrollment, and a small study of a new oral agent (CEM-101) is ongoing (NCT01591447). But the antibiotic pipeline is running dry: continued investment in antibiotic development is critical. Meanwhile, the gonococcus has continued to develop the capability to defeat each new antibiotic used. The threat of drug-resistant gonorrhea is increasing and has reached North America. Clinicians, drug developers, and public health professionals must act now.

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