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Sarah Kidd, Robert Kirkcaldy, Hillard Weinstock & Gail Bolan

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Tackling multidrug-resistant gonorrhea: how should we prepare for the untreatable?

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Sarah Kidd

Author for correspondence: Division of STD Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333, USA
Tel.: +1 404 639 8314
skidd@cdc.gov

Robert Kirkcaldy

Division of STD Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333, USA

Hillard Weinstock

Division of STD Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333, USA

Gail Bolan

Division of STD Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333, USA

"If cephalosporin resistance develops and spreads, successful treatment of gonorrhea will be extremely challenging, especially in settings without access to antimicrobial susceptibility testing to guide treatment decisions."

Control of *Neisseria gonorrhoeae* infection continues to represent a significant public health challenge worldwide. Globally, an estimated 88 million new cases of gonorrhea occur annually [1]. In addition to causing urethritis and cervicitis, *N. gonorrhoeae* infection can result in serious complications such as pelvic inflammatory disease, chronic pelvic pain, tubal infertility and ectopic pregnancy in women, and can facilitate HIV transmission [2]. Timely and effective treatment for gonorrhea prevents severe complications in the individual and limits transmission of the disease in the community by shortening the duration of infection. However, *N. gonorrhoeae* has progressively acquired resistance to each of the antimicrobial agents that have been recommended for treatment over the past 70 years, and the remaining treatment options are dwindling.

Since gonorrhea was first treated with sulfalinamide at the beginning of the antimicrobial era, *N. gonorrhoeae* has systematically developed resistance to sulfonamides, penicillins, tetracyclines and, most recently, the fluoroquinolones [3]. Third-generation cephalosporins are one of the last classes of antimicrobials that remain highly effective against gonorrhea. They are the recommended first-line treatment for gonorrhea in many countries, including the USA; however, there is evidence that cephalosporin-resistant *N. gonorrhoeae* may be on the horizon. The first reports of possible cephalosporin treatment failures associated with decreased *in vitro* susceptibility came from Japan during 2001–2003, and decreasing susceptibility of *N. gonorrhoeae* to third-generation cephalosporins has been observed in east Asia for more than 10 years [4]. Recently, cases of possible cefixime treatment failures in Europe were reported in 2010–2011 [5–9], and decreasing susceptibility to third-generation cephalosporins has been observed in Europe, Canada and the USA [10–12].

In the USA, the Gonococcal Isolate Surveillance Project (GISP) monitors antimicrobial susceptibilities in *N. gonorrhoeae* isolates obtained from approximately 5900 symptomatic men at 25–30 sexually transmitted disease clinics each year. Although the MIC breakpoints that correspond to cephalosporin resistance have not yet been defined, from 2006 to the first 6 months of 2011, the proportion of GISP isolates with elevated MICs of the oral cephalosporin cefixime (MIC ≥0.25 µg/ml) and the injectable cephalosporin ceftriaxone (MIC ≥0.125 µg/ml) increased from 0.1 to 1.7% and from 0.05 to 0.5%, respectively [13]. These increases were most marked in the western region of the USA and among men who have sex with men (MSM). In the western USA, the proportion of isolates with elevated cefixime MICs increased from 0.2 to 3.6% and the proportion

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with elevated ceftriaxone MICs increased from 0.04 to 1.9%. Among MSM, the proportion of isolates with elevated cefixime and ceftriaxone MICs increased from 0.2 to 4.7% and from 0 to 1.0%, respectively. The geographic progression of decreasing susceptibility to cephalosporins initially in east Asia and subsequently in Europe and North America, and the fact that patients in the western region and MSM are the first populations affected in the USA, are of particular concern, as these same patterns were observed during the emergence of fluoroquinolone-resistant *N. gonorrhoeae*.

Owing to the declining susceptibility of *N. gonorrhoeae* to cefixime, now ceftriaxone is the preferred cephalosporin for treatment of gonorrhea in many countries. However, in 2009, a gonococcal isolate with a ceftriaxone MIC of 2 µg/ml was identified in a Japanese female commercial sex worker with pharyngeal infection and possible ceftriaxone treatment failure [14], and in 2010, an isolate with a ceftriaxone MIC of 1–2 µg/ml was identified in France in a male with urogenital infection [5], suggesting that widespread gonococcal resistance to third-generation cephalosporins, including ceftriaxone, may be imminent.

The emergence of cephalosporin resistance would severely limit treatment options for *N. gonorrhoeae*. The WHO and other national health agencies have traditionally used the standard of ≥95% effectiveness for an antimicrobial to be considered a recommended treatment for gonorrhea [15], so that cephalosporins could no longer be recommended when the prevalence of cephalosporin resistance in gonococcal isolates reaches 5%. It is not known whether, or for how long, increased doses of cephalosporins could help maintain ≥95% clinical effectiveness of cephalosporins against *N. gonorrhoeae* in the setting of emerging resistance, and few other existing antimicrobials meet the ≥95% effectiveness standard. GISP data have demonstrated the persistence of penicillin, tetracycline and fluoroquinolone resistance in >5% of gonococcal isolates in the USA [16], so returning to the routine use of previously recommended treatments is not an option. High-dose azithromycin monotherapy (2 g as a single dose) is currently used as an alternative regimen for cephalosporin-allergic patients, but is not a viable long-term option for routine treatment owing to the ease with which *N. gonorrhoeae* develops macrolide resistance and given that cases of high-level azithromycin resistance and a recent azithromycin treatment failure case have been reported already [17–19]. Spectinomycin is not widely available, nor adequately effective against pharyngeal infection [20] and its resistance in *N. gonorrhoeae* has been reported in the past [21]. Gentamicin has been proposed as an alternative treatment option, but a recent meta-analysis found that single-dose treatment resulted in a pooled cure rate of 91.5% (95% CI: 88.1–94.0), failing to meet the current criteria of ≥95% effectiveness for recommended treatment for gonorrhea [22]. Thus, no existing antimicrobial is well suited to replace ceftriaxone as a recommended treatment for gonorrhea at all anatomic sites. If cephalosporin resistance develops and spreads, successful treatment of gonorrhea will be extremely challenging, especially in settings without access to antimicrobial susceptibility testing (AST) to guide treatment decisions.

Minimizing the impact of cephalosporin-resistant *N. gonorrhoeae* will require a concerted and sustained effort by medical and public health communities. For clinicians, it is essential to treat gonorrhea patients with the most effective treatment regimen currently available. In the USA, the CDC recommends dual therapy with ceftriaxone 250 mg as a single dose intramuscularly plus either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice a day for 7 days [12]. Dual therapy provides coverage against chlamydia or other copathogens, increases the likelihood of cure if the infecting organism is resistant to one of the antimicrobials used, and might inhibit the development of antimicrobial resistance caused by selective drug pressure by targeting the organism through two different mechanisms of action at the same time. Clinicians should be vigilant for possible cases of cephalosporin treatment failure, even when re-exposure and re-infection cannot be ruled out. Gonorrhea patients with persistent or recurrent symptoms shortly following treatment should receive a test of cure, preferably with culture and AST of any positive isolates, and public health authorities should be notified of any suspected treatment failures. Gonorrhea control and prevention measures, including screening of individuals at high risk of infection, prevention counseling that reduces risk through condom use and reduction in concurrent partnerships, and evaluation and treatment of sex partners, should be scaled up, as these may reduce the burden of disease and minimize the impact of cephalosporin resistance.

For public health officials, laboratory capacity and surveillance systems for monitoring antimicrobial-resistant gonorrhea must be strengthened and maintained. However, large gaps in the surveillance of antimicrobial-resistant gonorrhea exist globally, and certain regions do not have any available data on antimicrobial susceptibility trends in *N. gonorrhoeae*. Ideally, national or regional antimicrobial susceptibility data would inform treatment recommendations, identify the emergence of resistant gonorrhea in a timely manner and provide data so that global trends in antimicrobial-resistant gonorrhea can be monitored. Surveillance of antimicrobial resistance is dependent upon laboratories with capacity for gonorrhea culture and AST. Culture is required for AST, but is increasingly being replaced by nucleic acid amplification testing for the diagnosis of gonorrhea. Multiple genetic mutations associated with decreased susceptibility to cephalosporins have been identified, but it appears that a combination of mutations, some of which have not been identified, is required for resistance [4]. Until the molecular determinants of cephalosporin resistance are identified and reliable drug-specific molecular tests for antimicrobial resistance are developed, local capacity to perform culture and AST will remain critical for ongoing surveillance and for confirming antimicrobial resistance in suspected treatment failures and guiding individual treatment decisions. Furthermore, even if molecular tests for resistance become available, local culture and AST capacity will still be required for the surveillance of novel resistance. A strategic approach to strengthening culture and AST capacity should include communication with clinicians and laboratorians to increase awareness of the threat of antimicrobial-resistant gonorrhea, local assessment of private and public laboratory capacity for gonococcal culture and AST, and facilitation of access to gonococcal culture, either through referral systems or through increased availability of the appropriate culture plates and transport media.

Ultimately, there is an immediate need for new antimicrobials or antimicrobial combinations for the treatment of gonorrhea. A safe and effective vaccine would obviate this need, but is not expected to be an option for the foreseeable future. In the USA, one clinical trial is currently evaluating the effectiveness of two novel combinations of existing antimicrobials (gentamicin plus azithromycin and gemifloxacin plus azithromycin) for the treatment of gonorrhea, but additional studies are urgently needed. The limited number of new antimicrobials in the drug development pipeline represents a crisis for the treatment of both gonorrhea and many other serious or life-threatening bacterial infections. Public health authorities and government leaders need to work together at the policy level to facilitate the research and development required to replenish the antimicrobial pipeline.

The emergence of cephalosporin resistance in *N. gonorrhoeae* threatens gonorrhea control programs worldwide. If current trends continue, it is only a matter of time before cephalosporin resistance in *N. gonorrhoeae* becomes widespread. Clinicians, public health authorities and political leaders must now take action to limit the impact on public health.

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