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Antimicrobial Resistance in *Neisseria gonorrhoeae*

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INTRODUCTION

Gonorrhea is the second most commonly reported notifiable disease in the United States. In 2012, a total of 334,826 gonorrhea cases were reported nationwide to the Centers for Disease Control and Prevention (CDC).[1] However, case detection and case reporting are known to be incomplete, and it is estimated that the true number of new gonococcal infections in the United States exceeds 800,000 per year.[2] Adolescents aged 15 to 19 years and young adults aged 20 to 24 years are disproportionately affected by gonorrhea; they accounted for 58.7% of all gonorrhea cases reported in the United States in 2012. As in previous years, the 2012 gonorrhea rates among adolescents (376.8 cases per 100,000 population) and young adults (520.1 cases per 100,000 population) were significantly greater than the overall national rate (107.5 cases per 100,000 population).

Neisseria gonorrhoeae can infect the urogenital tract, rectum, oropharynx, and conjunctivae, and it is transmitted almost exclusively through sexual contact or perinatally.[3] Urogenital infection may be associated with dysuria and urethral discharge in males or cervical discharge in females, but most urogenital infections in females and a substantial minority in males are asymptomatic.[3–5] Rectal infection most often is asymptomatic but may be associated with rectal pain, discharge, bleeding, or tenesmus.[3] Similarly, pharyngeal infection most often is asymptomatic but may be associated with sore throat or pharyngeal exudate.[3] Disseminated gonorrhea is rare, occurring in less than 3% of untreated acute gonococcal infections, but it can be life threatening when complicated by endocarditis or meningitis.[3] More common complications of gonococcal infection include pelvic inflammatory disease, tubal infertility, and ectopic pregnancy, as well as facilitated transmission and acquisition of human immunodeficiency virus (HIV).[3,6]

The timely administration of effective treatment for infected patients and their partners, preferably in the form of a single-dose regimen, has been a critical tool for gonorrhea control efforts. Timely and effective treatment limits the duration of infection in affected individuals, thereby minimizing transmission to others and risk of complications within the infected individual. For these reasons, CDC has historically recommended only treatment

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regimens that are at least 95% effective against *N gonorrhoeae* infection.[7] However, the number of highly effective treatment options for gonorrhea is diminishing because *N gonorrhoeae* has proven to be adept at developing antimicrobial resistance. *N gonorrhoeae* has progressively acquired resistance to each of the antimicrobials previously recommended as first-line treatment of gonorrhea, leaving only 1 regimen that is currently recommended by CDC: dual treatment with ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally.[8] As gonococcal susceptibility to cephalosporins has declined over the last decade, the emergence of gonococcal resistance to cephalosporins, including ceftriaxone, seems inevitable. Antimicrobial-resistant *N gonorrhoeae* has been declared an urgent public health threat, and experts are warning that an era of "unbeatable" gonorrhea maybe on the horizon.[9,10] This article refers to the management of adolescents by physicians, physician assistants, nurse practitioners, and other health care providers, hereinafter referred to as "clinicians" Clinicians and public health officials should be aware of the threat of cephalosporin-resistant gonorrhea and should take action now to mitigate its effect on patients and public health.

HISTORY OF GONOCOCCAL ANTIMICROBIAL RESISTANCE IN THE UNITED STATES

Resistance to Sulfonamides, Penicillin, and Tetracycline

Gonorrhea treatment and control have been complicated by antimicrobial resistance ever since the introduction and widespread use of antimicrobials in the 1930s. The first class of antimicrobials to be introduced, the sulfonamides, revolutionized the management of patients with gonorrhea, but treatment failures were common.[11] By 1944, it was reported that approximately 30% of patients with uncomplicated gonorrhea failed to respond to the standard 5- to 7-day course of sulfonamide therapy, and 15% to 20% also failed a second course of therapy.[12] When penicillin became available in the 1940s, it quickly replaced the sulfonamides as the drug of choice for treatment of gonorrhea.[12,13] However, gonococcal susceptibility to penicillin gradually declined from 1945 to 1969 as the result of the accumulation of multiple chromosomal mutations.[14–16] This decline in penicillin susceptibility prompted progressive increases in the recommended therapeutic dose, from a total dose of 50,000 to 200,000 units in the mid-1940s to 4.8 million units in 1972.[12,13,17–20] The addition of probenecid, to be coadministered with penicillin, was recommended by the early 1970s to maintain penicillin's efficacy against *N gonorrhoeas*.[20,21] High-level penicillin resistance, conferred by plasma-mediated production of penicillinase and resistance to even the highest doses of penicillin, was first reported in 1976 in the United States in 2 patients who acquired gonococcal urethritis in the Philippines.[22,23] In the same year, a different strain of penicillinase-producing *N gonorrhoeae* (PPNG), linked to West Africa, was reported from the United Kingdom.[24–26] Within a few years, PPNG had been identified throughout the world, and multiple outbreaks had been reported in the United States.[27,28] By 1989, resistance to penicillin, both PPNG and chromosomally mediated *N gonorrhoeae*, was widespread throughout the United States, and penicillin was no longer recommended for treatment of gonorrhea.[29] In the meantime, tetracycline had become available and was added as a recommended regimen for gonorrhea treatment in 1978.[30] However, gonococcal resistance to tetracycline increased alongside resistance to penicillin, and high-level tetracycline resistance was soon detected in the United States.[31–33] By 1985,

tetracycline was no longer recommended as a first-line gonorrhea treatment regimen.[34] Ceftriaxone was added as a first-line regimen in 1985, and when penicillin was no longer recommended in 1989, ceftriaxone became the only recommended treatment of gonorrhea.[29,34] Oral fluoroquinolones (ciprofloxacin and ofloxacin) and cefixime (an oral third-generation cephalosporin) were first added as recommended first-line regimens in 1993.[35]

The US Gonococcal Isolate Surveillance Project

As concerns about antimicrobial-resistant gonorrhea grew in the 1980s, in 1986 the CDC established a national sentinel surveillance system to monitor gonococcal resistance in the United States, the Gonococcal Isolate Surveillance Project (GISP).[36] GISP collects approximately 5000 to 6000 urethral isolates per year from symptomatic men attending sexually transmitted infection clinics in 25 to 30 cities throughout the United States. GISP has monitored trends in gonococcal susceptibility to penicillin, tetracycline, ciprofloxacin, and other antimicrobials over time (Figure 1) and has provided a rational basis for determining which treatment regimens the CDC should recommend.

Fluoroquinolone Resistance

GISP data, in conjunction with supplemental susceptibility data provided by state and local health departments, were instrumental in detecting and documenting the emergence of fluoroquinolone resistance in the United States. In the early 1990s, fluoroquinolone resistance was emerging in Asia and the Western Pacific and had already been detected in Hawaii in patients who had recently traveled to or whose sex partners had recently traveled to Southeast Asia.[37–39] Sporadic cases of fluoroquinolone resistance were detected in the United States throughout the 1990s, and gradually became more common, primarily in Hawaii and on the West Coast.[40–42] By 1999, 14.3% of GISP isolates from Honolulu exhibited resistance to fluoroquinolones, compared with 0.2% of isolates obtained from the continental United States and Alaska, and in 2000 fluoroquinolones were no longer recommended for gonorrhea treatment in Hawaii.[42,43] Shortly after, similar increases were observed in California, and fluoroquinolones were no longer advised in California in 2002.[44,45] Over the next few years, fluoroquinolone resistance became widespread throughout the United States, first among men who have sex with men (MSM) and then among heterosexuals,[46,47] so in 2007 fluoroquinolones were no longer recommended for treatment of gonorrhea anywhere in the United States. This again left the third-generation cephalosporins (intramuscular [IM] ceftriaxone or oral cefixime) as the only remaining class of drugs recommended for treatment of gonorrhea.[47]

DECLINING GONOCOCCAL SUSCEPTIBILITY TO CEPHALOSPORINS

Worryingly, there is evidence that *N gonorrhoeae* is beginning to develop resistance to cephalosporins. Although the in vitro susceptibility breakpoint that correlates with clinically significant cephalosporin resistance has not yet been defined, at the population level, the minimum inhibitory concentrations (MICs) of cephalosporins required to inhibit *N gonorrhoeae* growth in the laboratory have been increasing in Asia for more than a decade and more recently in Australia, Europe, Canada, and the United States, indicating gonococcal susceptibility to cephalosporins is declining in these regions.[48–52]

Cases of cefixime treatment failures associated with laboratory evidence of reduced susceptibility have been detected in Asia since 1999, in Europe and Canada since 2010, and in South Africa in 2012.[53–61] Of most concern, cases of ceftriaxone treatment failure and resistance have now been reported in Japan, France, and Spain. In 2009, a gonococcal isolate obtained from the pharynx of a female commercial sex worker in Japan who failed to respond to a 1-g dose of ceftriaxone intravenously was found to have an MIC of 2 to 4 mcg/mL, an MIC that is significantly higher than any previously described ceftriaxone MIC.[62,63] In 2010 and 2011, a second strain of *N gonorrhoeae* with high ceftriaxone MICs (1–2 mcg/mL) was detected in 3 MSM in France and Spain.[59,64]

Multiple chromosomal mutations are associated with reduced susceptibility to cephalosporins, including mutations in *penA*, which encodes penicillin-binding protein 2, the primary target for the cephalosporins; *mtrR*, which alters expression of an efflux pump and affects efflux of antimicrobials from the bacterial cell; *penB*, which encodes an outer membrane protein channel that affects drug entry; and at least 1 other unknown determinant, termed "factor X."[65] High-level cephalosporin resistance seems to result from the combined effect of these mutations, the most important of which *is penA*. Many strains of *N gonorrhoeae* with reduced susceptibility to cephalosporins contain regions of *penA* genes (mosaic *penA*) apparently acquired from commensal *Neisseria* species commonly residing in the oropharynx, suggesting that pharyngeal gonococcal infections may provide the opportunity for horizontal transfer of DNA and resistance mutations between *Neisseria* species.

Although no cefixime or ceftriaxone treatment failures have been documented in the United States, the proportion of GISP isolates with elevated cefixime and ceftriaxone MICs increased during 2000 to 2011. The proportion of GISP isolates with elevated cefixime MICs (MIC ≥0.25 mcg/mL) was stable at 0.1% to 0.2% during 2000 to 2006 but increased to 1.4% in 2010 and 2011 (Figure 2).[1,52] The proportion of GISP isolates with elevated ceftriaxone MICs (MIC ≥0.125) has remained low but increased from 0.1% in 2000 to 0.3% in 2010 and to 0.4% in 2011 (Figure 2).[1,52] As was seen with the emergence of fluoroquinolone resistance, during 2000 to 2010 the greatest increases in cefixime MICs were seen in the West and among MSM.[52] In the West, the proportion of isolates with elevated cefixime MICs increased from 0% in 2000 to 3.3% in 2010 but remained 0.5% or less in other regions of the country. Among MSM, the proportion of isolates with elevated cefixime MICs increased from 0% in 2000 to 4.0% in 2010. In comparison, among men who have sex exclusively with women (MSW), the proportion of isolates with elevated MICs remained less than 0.5%. The greatest increases in MICs were observed among MSM in the West and Midwest.

Because of the observed declines in susceptibility to cephalosporins, particularly cefixime, globally and in the United States in the previous decade, the CDC began recommending dual therapy (either ceftriaxone or cefixime plus either azithromycin or doxycycline) for all cases of gonorrhea in 2010.[66] In 2012, recommendations were revised once again, and cefixime was no longer recommended as a first-line regimen for treatment of gonorrhea.[67]

In 2012, the most recent year for which complete GISP data are available, the proportion of GISP isolates with elevated cephalosporin MICs decreased slightly compared with 2011 (Figure 2): 1.0% had elevated cefixime MICs, and 0.3% had elevated ceftriaxone MICs.[1] Although it is encouraging that cephalosporin MICs did not continue to increase in 2012, it will be important to monitor gonococcal susceptibility to cephalosporins closely in the coming years.

RECOMMENDED TREATMENT OF UNCOMPLICATED GONOCOCCAL INFECTION

Recommended Regimen

As of 2014, the only recommended first-line treatment regimen for uncomplicated gonococcal infection in adolescents and adults is dual therapy with ceftriaxone 250 mg in a single IM dose plus azithromycin 1 g orally in a single dose.[8] Because of the high prevalence of tetracycline resistance among GISP isolates, particularly among those with elevated cefixime MICs, azithromycin is now preferred over doxycycline as the second antimicrobial. Dual therapy minimizes the risk of transmission of resistant *N gonorrhoeae* as long as the organism is susceptible to at least 1 of the antimicrobials used and may hinder development of resistance by targeting *N gonorrhoeae* through more than 1 mechanism of action. Azithromycin also provides coverage for chlamydial coinfection, which is common among patients with gonorrhea.[68] Ceftriaxone and azithromycin should be administered together, preferably simultaneously and under direct observation. For clinical settings that do not dispense oral medications on site, prescriptions for azithromycin should be accompanied by patient instructions to fill the prescription and take azithromycin as soon as possible.

Alternative Regimen

If ceftriaxone is not available, dual treatment with cefixime 400 mg orally as a single dose plus azithromycin 1 g orally as a single dose is recommended as an alternative regimen for patients with uncomplicated urogenital or rectal gonorrhea. Pharyngeal infections are more difficult to eradicate, and ceftriaxone is clearly more effective than cefixime for treatment of gonococcal infection of the pharynx, with a 99% cure rate (95% confidence interval [CI] 94.4%–100%) for ceftriaxone compared with a 92.3% cure rate (95% CI 74.9%–99.1%) for cefixime.[69] Therefore, cefixime or cefixime-based regimens are not recommended for treatment of pharyngeal gonorrhea.

A recent clinical trial of patients aged 15 to 60 years demonstrated the effectiveness of 2 new dual-therapy regimens for urogenital gonococcal infection: gemifloxacin 320 mg orally plus azithromycin 2 g orally (99.5% cure rate, lower 1-sided 95% CI bound = 97.5%), and gentamicin 240 mg intramuscularly plus azithromycin 2 g orally (100% cure rate, lower 1-sided 95% CI bound = 98.5%).[70] These regimens may be considered as additional alternative regimens for treatment of uncomplicated urogenital gonorrhea if ceftriaxone is not available. Both regimens cured the small numbers of rectal and pharyngeal infections included in the trial, but the trial was not powered to estimate the efficacy of these regimens for extragenital infections. Additionally, the gastrointestinal side effects associated with these regimens may limit their use in many settings. Overall, 7.7% of patients treated with

gemifloxacin plus azithromycin and 3.3% of patients treated with gentamicin and azithromycin vomited within 1 hour and required retreatment with a different regimen.

Other Antimicrobials

Higher-dose azithromycin (2 g) is effective as monotherapy against uncomplicated urogenital and rectal *N gonorrhoeae* infection. The proportion of GISP isolates with elevated azithromycin MICs has remained less than 1%, with no apparent temporal trend.[1,71,72] However, azithromycin monotherapy is not recommended because of the ease with which *N gonorrhoeae* develops resistance to macrolide antimicrobials, and because high-level azithromycin resistance has already been detected on multiple continents, including North America.[73–77] Because resistance to penicillin, tetracycline, and ciprofloxacin has persisted in the United States, returning to empiric use of any of these previously recommended antimicrobials as a first-line treatment regimen is not an option. In 2012, 13.1% of GISP isolates were resistant to penicillin, 23.5% were resistant to tetracycline, and 14.7% were resistant to ciprofloxacin.[1] Spectinomycin is effective for treatment of urogenital and rectal infections, but it does not reliably cure pharyngeal infections and is not currently available in the United States, and resistance has emerged rapidly when it has been widely used in the past[69,78] Monotherapy with gentamicin has been considered as a potential treatment option, but a recent meta-analysis demonstrated a pooled cure rate of 91.5% (95% CI 88.1%–94.0%) for urogenital gonorrhea and therefore was not sufficiently effective to be recommended on its own.[79]

Management of Sex Partners

Clinical management of a patient with gonorrhea must include appropriate treatment of the patient's recent sex partners (any partners within the 60 days preceding a patient's onset of symptoms or diagnosis of gonorrhea) in order to prevent reinfection of the index patient and to prevent further transmission in the community. Ideally, sex partners would be evaluated in a clinic-based setting and treated with the recommended regimen of ceftriaxone plus azithromycin. However, in states where expedited partner therapy (EPT) for gonorrhea is permissible and if prompt evaluation and treatment cannot be assured, EPT with the alternative regimen (cefixime plus azithromycin), delivered to the partner by the patient, disease investigation specialist, or collaborating pharmacy, should be offered to females and heterosexual males. EPT is not recommended as a routine partner management strategy for partners of MSM because of the high risk of undiagnosed sexually transmitted infection or HIV coinfection. Legal status of EPT by state is available at www.cdc.gov/std/ept/legal.

DETECTION AND DIAGNOSIS OF ANTIMICROBIAL-RESISTANT GONORRHEA

Detection of antimicrobial resistant gonorrhea begins with detection of gonorrhea. Patients with genitourinary symptoms or physical examination findings consistent with urethritis/cervicitis, and those who report having had sexual contact with a person recently diagnosed with gonorrhea, should be tested for *N gonorrhoeae* infection at the anatomic site(s) of exposure (urogenital tract, rectum, and/or pharynx). Because urogenital gonococcal infection in females frequently is asymptomatic, the CDC, the US Preventive Services Task Force,

and the American Academy of Pediatrics (AAP) recommend annual screening for gonococcal infection for all sexually active females who are at increased risk for infection.[8,80,81] Females younger than 25 years, including sexually active adolescents, are at highest risk for gonococcal infection.[1] Other risk factors for gonococcal infection include previous history of gonococcal infection, other sexually transmitted infections, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use.[8,80] The CDC also recommends screening MSM at least annually for gonococcal infection at all anatomic sites of exposure.[8]

Nucleic acid amplification tests (NAATs) have largely replaced gonococcal culture for gonorrhea diagnosis in most clinical settings.[82] NAATs are more sensitive than culture for detecting *N gonorrhoeae*, have comparable specificity, and can be performed on a wider variety of specimen types, including urine.[83–88] In addition, compared with gonococcal culture, NAATs have less stringent storage and transport requirements. Although NAATs have not been cleared by the US Food and Drug Administration (FDA) for use at pharyngeal and rectal sites, some public and commercial laboratories, including laboratories such as Quest and LabCorp, have conducted verification studies, allowing use of these tests for clinical management. Unfortunately, at present, antimicrobial susceptibility testing cannot be conducted on NAAT specimens. As a result, the increased use of NAATs, accompanied by diminished access to gonococcal culture, has complicated detection and confirmation of antimicrobial resistance in *N gonorrhoeae*.

Few clinical settings continue to use culture for the routine diagnosis of gonorrhea, and antimicrobial susceptibility testing is generally not routinely conducted outside of surveillance programs. Therefore, in order to detect cephalosporin-resistant gonorrhea, clinicians must be vigilant for possible cephalosporin treatment failures. Clinicians should suspect gonorrhea treatment failure and resistance in patients who have persistent or recurrent symptoms and who report no re-exposure following treatment with the recommended regimen. For patients who report their partners have been treated, clinicians should take a careful history that includes timing of patient and partner treatment and resumption of sexual activity. Detection of treatment failure or resistance in patients with asymptomatic infection requires a test of cure. Routine test of cure currently is not recommended for patients who receive the recommended first-line regimen, but test of cure is recommended for patients with pharyngeal gonorrhea who are treated with an alternative regimen.[8] If culture is used, test of cure may be performed 7 days after treatment. The optimal timing of test of cure using a NAAT is not yet clear. If performed too soon after treatment, NAATs can detect nonviable nucleic acids that persist after eradication of infection, causing a false-positive NAAT result.[89,90] For this reason, the current CDC recommendation is to perform test of cure 14 days after treatment if a NAAT is being used.[19]

MANAGEMENT OF SUSPECTED CEPHALOSPORIN TREATMENT FAILURE OR RESISTANCE

Clinicians who suspect cephalosporin treatment failure or resistance based on clinical history or laboratory data should report these cases to the CDC through the local or state health department within 24 hours of diagnosis and should consult a specialist in infectious diseases, the local or state health department, or the CDC for advice on obtaining cultures, antimicrobial susceptibility testing, and appropriate treatment. Guidance regarding which laboratories can process clinical *N gonorrhoeae* culture specimens is best obtained from the local or state health department. Patients with suspected cephalosporin treatment failure should be retested for *N gonorrhoeae* using culture, preferably with simultaneous NAAT, at exposed anatomic sites. If gonococcal culture is positive, *N gonorrhoeae* isolates should be tested for antimicrobial susceptibility and retained for possible additional testing.

Because suspected treatment failures following treatment with the recommended regimen (dual treatment with IM ceftriaxone 250 mg plus oral azithromycin 1 g) are most likely to be reinfections, retreatment with the recommended regimen should be given in most cases. Patients with suspected treatment failure after treatment with an alternative regimen (oral cefixime 400 mg plus oral azithromycin 1 g) should be treated with IM ceftriaxone 250 mg plus oral azithromycin 2 g. For patients in whom treatment failure is likely because of cephalosporin resistance (eg, the collected isolate exhibits elevated cephalosporin MICs, the patient reports no reexposure and fails a second course of the recommended regimen, or the patient has other evidence of exposure to cephalosporin-resistant *N gonorrhoeae*), dual treatment with oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with IM gentamicin 240 mg plus oral azithromycin 2 g may be considered. A test of cure should be conducted 7 to 14 days after retreatment, preferably using culture. Identifying and treating sex partners of patients with suspected treatment failure is a priority. Sex partners within the 60 days preceding the initial onset of symptoms or diagnosis of gonorrhea in the patient, as well as any sex partners since the initial diagnosis, should be evaluated for *N gonorrhoeae* infection by culture and antimicrobial susceptibility testing and treated as indicated.

PUBLIC HEALTH RESPONSE TO THE THREAT OF CEPHALOSPORIN RESISTANCE

In the absence of new treatment options, cephalosporin-resistant gonorrhea would significantly impair gonorrhea control in the United States and worldwide. A key component of the public health response to resistant gonorrhea is strengthening surveillance for gonococcal susceptibility and improving the ability to detect emerging antimicrobial resistance. To do so, local laboratory capacity for gonococcal culture and antimicrobial susceptibility testing must be rebuilt. As a national sentinel surveillance system, GISP samples approximately 2% of all gonorrhea cases reported nationally, so large gaps in surveillance exist throughout the country. Local access to gonococcal culture and antimicrobial susceptibility testing are critical not only for enhancing local surveillance but also for confirmation of resistance in suspected treatment failures and for informing

treatment decisions for patients who are not successfully treated with a CDC-recommended regimen. Health departments are encouraged to assess which local laboratories perform gonococcal culture and antimicrobial susceptibility testing and to facilitate linkages between these laboratories and clinics, either through referral systems or through increased availability of the appropriate culture plates or transport media.

A second component of the public health response is increasing general gonorrhea prevention and control activities that reduce the overall gonorrhea disease burden. Clinicians play an important role in this strategy, which includes screening high-risk populations, such as females younger than 25 years and MSM, to identify new infections; assuring that patients are treated quickly with the most effective regimen available; evaluating and treating patients' sex partners; and providing risk-reduction counseling. When cases of suspected cephalosporin treatment failure or cephalosporin resistance are identified, health departments should prioritize these cases for investigation, report them to the CDC, and work with clinicians to facilitate evaluation and appropriate treatment of the sex partners of these cases.

In the long run, successful gonorrhea control will require new antimicrobials or antimicrobial combinations that are effective against *N gonorrhoeae*. Unfortunately, the number of new antimicrobials developed and approved has decreased significantly over the last 30 years, and few new antimicrobials are in the development pipeline.[9] Just 2 new antimicrobials, solithromycin and delafloxacin, have entered clinical trials for treatment of gonorrhea.[91,92] A fluoroketolide, solithromycin has greater in vitro potency against *N gonorrhoeae* than other macrolides, including azithromycin; it also has high in vitro activity against cephalosporin-resistant and multidrug-resistant strains, and the results of early clinical trials are promising.[93] Delafloxacin, a novel fluoroquinolone, exhibits high in vitro activity against *N gonorrhoeae*, including ciprofloxacin-resistant isolates.[94] Additional treatment options are urgently needed. Promoting the development of new antimicrobials for gonorrhea must be a priority.

CONCLUSION

Given previous experience with other classes of antimicrobials, it seems inevitable that gonococcal resistance to cephalosporins, including ceftriaxone, eventually will emerge in the United States, severely limiting treatment options and impairing gonorrhea control. Because adolescents and young adults are the age groups most affected by gonorrhea, they and their clinical providers are on the frontlines of the public health battle to delay the emergence and mitigate the effect of cephalosporin resistance. It is critical that clinicians providing care for adolescents and young adults screen high-risk populations to identify gonococcal infections, treat patients infected with *N gonorrhoeae* and their partners with the most effective regimen available, maintain vigilance for cephalosporin treatment failures, and team with public health officials to assure the early detection and rapid response to suspected cephalosporin treatment failure or resistance.

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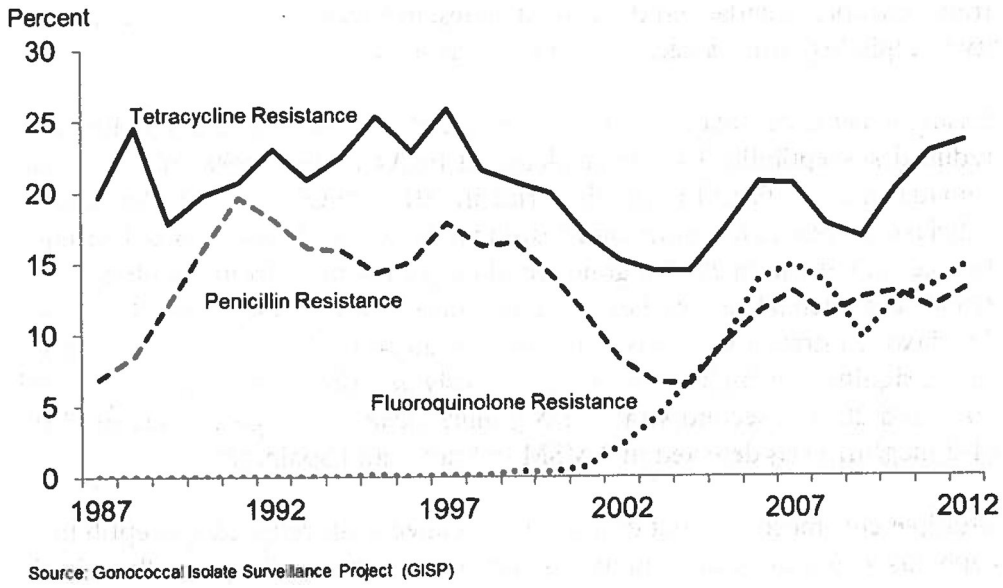

Fig 1.

Prevalence of penicillin, tetracycline, and fluoroquinolone resistance in urethral *Neisseria gonorrhoeae* isolates in the United States, 1987–2012.

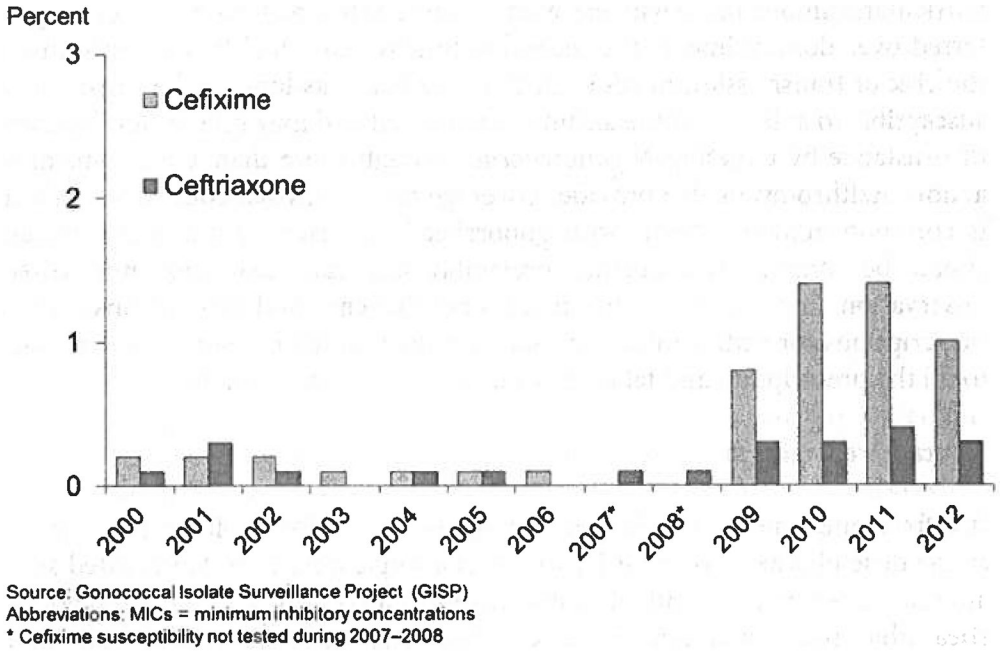

Fig 2.

Prevalence of urethral *Neisseria gonorrhoeae* isolates with elevated cefixime minimum inhibitory concentrations (MICs) (MIC ≥0.25 mcg/mL) and elevated ceftriaxone MICs (MIC ≥0.125 mcg/mL) in the United States, 2000–2012.