Addressing *Neisseria gonorrhoeae* Treatment Resistance With the DNA Gyrase A Assay: An Economic Study, United States

Adriane Wynn, PhD and Jeffrey D. Klausner, MD, MPH†*

Abstract: Targeted antibiotics could delay emergence of resistant *Neisseria gonorrhoeae*. The DNA gyrase subunit A assay predicts susceptibility to ciprofloxacin. A model found that adding a $50 gyrase subunit A test for asymptomatic patients screened for *N. gonorrhoeae* resulted in cost neutrality. When ciprofloxacin susceptibility was high, a $114 test resulted in savings.

BACKGROUND

According to the United Nations, "antimicrobial resistance is one of the greatest threats we face as a global community."[1] Globally, more than 700,000 people die each year because of drug-resistant diseases, and common diseases, such as those caused by sexually transmitted infections (STIs), are becoming untreatable.[2] The US Centers for Disease Prevention and Control declared multidrug-resistant *Neisseria gonorrhoeae* (NG) infections one of the top 3 antibiotic resistance threats.[3] There are cases of NG infections resistant to all antibiotic classes used for treatment.[4] Third-generation cephalosporins are the last reliable class of antibiotics recommended as first-line treatment.[5] No new classes of antibiotics are currently available.[6] A few new candidate compounds are in clinical development. One study found that gentamicin plus azithromycin cured 100% of 202 individuals with uncomplicated urogenital NG, and gemifloxacin plus azithromycin cured 99.5% of 199 infected individuals.[7] Another study found that single-dose zoliflodacin cured 109 (96%) of 113 individuals with urogenital NG.[8]

The current control strategy for NG is to reduce the overall burden by expanding screening and treatment[9,10]; however, the impact of this strategy in terms of reducing resistance is unclear.[11] A recent modeling study found that higher population treatment rates result in the faster spread of NG antibiotic resistance through the direct selection of antimicrobial-resistant infections.[11] In response, various strategies have emerged to combat resistance, including the development of molecular assays to predict NG antibiotic resistance.

Assays that predict antimicrobial susceptibility have allowed for the targeted use of antibiotics previously effective but no longer recommended. An example is the DNA gyrase subunit A (*gyr*A) assay, which detects mutations of the *gyr*A gene specific to NG. Investigators have shown that assays to predict susceptibility to ciprofloxacin can have high accuracy and reliability.[12,13] In the United States, it is estimated that approximately 70% of NG infections are susceptible to ciprofloxacin.[3] Therefore, the use of targeted therapy with ciprofloxacin could help reduce the selection pressure caused by the sole use of extended-spectrum cephalosporins to treat gonorrhea and potentially delay the emergence of ceftriaxone resistant NG.[14]

Although the use of targeted therapy could increase the control of treatment resistant NG infections, the cost of the additional molecular susceptibility testing is an important consideration. The aim of this study was to identify the price point at which the additional cost of the *gyr*A assay would either break even or generate cost savings compared with the current standard of care (no *gyr*A testing).

METHODS

We conducted a cost analysis to identify the price point at which adding the *gyr*A assay to NG management would either break even or yield cost savings compared with the standard of care in the United States. We used a hypothetical cohort of 10,000 asymptomatic individuals seeking STI screening in the United States. Our model included 2 diagnostic pathways, based on a review of the literature and expert clinical guidance. We took a health care perspective. We expressed all costs in 2019 US dollars, and there was no discounting because of a short time frame.

In each arm, all asymptomatic individuals seeking screening received NG testing and those with negative results received no treatment. In the standard of care, all patients with NG positive results received dual therapy (250-mg injection of ceftriaxone and 1000-mg oral dose of azithromycin) per current Centers for Disease Prevention and Control guidelines.[5] In the *gyr*A arm, laboratorians tested specimens positive for NG infection for ciprofloxacin susceptibility with the *gyr*A assay. Patients with predicted susceptibility to ciprofloxacin (wild-type *gyr*A) received 500 mg ciprofloxacin orally in place of dual therapy. Those without susceptible infections (non–wild-type *gyr*A) received dual therapy.

Model parameters are included in Table 1. Test sensitivities and specificities for the GeneXpert (Cepheid, Sunnyvale, CA) and the *gyr*A assay were identified from validation studies[15] and a systematic review,[12] respectively. We obtained treatment costs from the Centers for Medicare & Medicaid fee schedule[17] and the National Average Drug Acquisition Cost data set.[16] We assumed that clinicians could prescribe ciprofloxacin electronically or over the telephone and thus included only the medication cost (i.e., no repeat clinical visit). We also did not consider dispensing fees because these are likely to be equal between the 2 arms. Dual therapy included the costs of azithromycin, ceftriaxone, an injection procedure, and a repeat clinical visit (low-level office/outpatient visit for established patients). Costs associated with the index office visit, which may have also included the diagnosis and treatment of *Chlamydia trachomatis* and other STIs,

From the *Division of Infectious Diseases and Global Public Health, University of California, San Diego, San Diego; and †Departments of Medicine and Epidemiology, University of California, Los Angeles, Los Angeles, CA

Conflict of Interest and Sources of Funding: This project was funded in part by SpeedX LTD. The authors report no other conflicts.

Correspondence: Adriane Wynn, PhD, Division of Infectious Diseases and Global Public Health, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093. E-mail: awynn@ucsd.edu.

Received for publication July 9, 2019, and accepted October 21, 2019.
DOI: 10.1097/OLQ.0000000000001090

TABLE 1. Model Probabilities Included in Cost Minimization Model Comparing Conventional NG Management With the Addition of *gyr*A Testing

	Base	Range	Reference
Probabilities			
Prevalence of NG (asymptomatic), %	2	0.5–8	CDC[3]
Sensitivity (GeneXpert), %	100	87–100	Gaydos[15]
Specificity (GeneXpert), %	99	99–100	Gaydos[15]
Susceptibility to ciprofloxacin, %	70	55–95	CDC[3]
*gyr*A sensitivity, %	98	97–99	Allan-Blitz[12]
*gyr*A specificity, %	99	97–99	Allan-Blitz[12]
Costs			
Ciprofloxacin (500 mg oral), $	0.12	0.06–0.24	NADAC[16]
Ceftriaxone (250 mg IM)*, $	2.18	1.09–4.36	NADAC[16]
Injection procedure (HCPCS code 96372), $	16.94	8.47–33.88	HCPCS[17]
Azithromycin (1000 mg oral), $	2.78	1.39–5.56	NADAC[16]
Follow-up visit (HCPCS code 99213), $	52.20	0–100	HCPCS[24]

*Costs were only available for the 1-g vial ceftriaxone.

CDC indicates Centers for Disease Prevention and Control; *gyr*A, gyrase subunit A; HCPCS, Healthcare Common Procedure Coding System; IM, intramuscular; NADAC, National Average Drug Acquisition Cost; NG, *N. gonorrhoeae*.

were included in both arms; therefore, we did not consider them in the cost analysis.

For the analysis, first, we held the parameters at baseline levels for the general population and varied the additional cost of adding *gyr*A testing to identify the breakeven point (when the additional cost of the test was balanced by treatment savings) between the standard-of-care strategy and the reflex *gyr*A strategy. Next, we varied the prevalence of NG infection, ciprofloxacin susceptibility, and the cost of a standard-of-care follow-up visit to assess how the breakeven cost would vary when implemented in low- and high-risk populations.[3] Finally, we assessed all scenarios assuming that 30% of *gyr*A test results were indeterminate.

RESULTS

In the *gyr*A testing arm, 200 of the 10,000 patients tested positive for NG, 140 were susceptible, 137 were accurately identified as susceptible by the test, 1 was incorrectly identified as susceptible, 138 were treated with ciprofloxacin, and 62 with dual therapy. The average cost of dual therapy per patient was approximately $72, and the total cost of treating a hypothetical sample of 10,000 patients (2% NG positivity) was $14,380. If we tested all NG-infected patients with a *gyr*A assay, the breakeven point (where the cost of adding *gyr*A testing was offset by treatment savings) was a $50 per test. Less than $50 per *gyr*A test would be cost-saving.

As seen in Table 2, as the prevalence of ciprofloxacin susceptibility and the cost of the standard-of-care follow-up visits increase, the breakeven cost of adding the *gyr*A assay also increases (ranging from $12 to $114 per test). Varying the NG prevalence did not significantly impact the breakeven point, as an increase in NG cases would raise the total costs of both the standard-of-care and the *gyr*A scenarios similarly. If we assumed that 30% of tests are indeterminant, the new breakeven cost was $35/test for the base case and ranged from $8 to $79 in the other scenarios.

DISCUSSION

We found that adding *gyr*A testing to predict ciprofloxacin susceptibility for asymptomatic patients being screened for NG infection at an additional cost of $50 per test would result in a breakeven point between the test costs and treatment savings. *Gyr*A testing costs less than $50 per test would be cost saving. In scenarios where the ciprofloxacin susceptibility level was high, adding the *gyr*A test up to price point of $114 still resulted in overall cost neutrality.

Our analysis considered impacts on the direct medical costs of treatment; however, it is also important to consider the potential benefits to society of reducing NG treatment resistance. Treatment-resistant NG could result in increased incidence of gonococcal infections through several factors, including increased duration of infection.[18,19] Furthermore, a rise in NG incidence could have important implications in terms of decreasing the quality of life and productivity of those infected, increasing the probability of gonorrhea-attributable HIV infection, mother-to-child transmission of NG, and increasing health care costs.[20,21] For example, one study found that, during a 10-year period, emerging NG resistance could result in 1.2 million additional NG infections and 579 gonorrhea-attributable HIV infections, for a total cost of $378.2 million.[22]

Our study has several limitations. To estimate patient treatment and medical visit costs, we used the national payment amounts

TABLE 2. *gyr*A Assay Breakeven Point (2019 USD) by Varying Ciprofloxacin Susceptibility With Follow-Up Visit Cost

		Ciprofloxacin Susceptibility			
Follow-up Visit Cost	**NG Prevalence**	**55%**	**70%**	**85%**	**95%**
$0	2%	$12	$15	$18	$20
	8%	$12	$15	$18	$20
$50	2%	$39	$50	$60	$67
	8%	$39	$50	$60	$67
$100	2%	$67	$84	$102	$114
	8%	$67	$84	$102	$114

*gyr*A indicates gyrase subunit A; NG, *Neisseria gonorrhoeae;* USD, US dollars.

provided by the Centers for Medicare & Medicaid physician fee schedule, which may not be generalizable to all localities and health care facilities. Furthermore, those are benchmark dollar values for reimbursement and may not reflect the actual cost incurred by health facilities for performing tasks or acquiring drugs. Thus, it is possible that our analysis reflects an underestimation of the cost of dual therapy. In addition, our algorithm assumes that patients prescribed ciprofloxacin do not return for follow-up medical visit, which would result in cost savings compared with dual therapy where a second visit is required. However, that may not represent the clinical practice at all sites. Furthermore, we do not consider differential treatment uptake and time to treatment between the 2 arms. It may be that patients are less likely to receive timely treatment when faced with the potential burden of an additional office visit. If that is the case, the short-term costs of the no *gyr*A testing arm may be lower than what we present. However, if our results in terms of numbers treated were to be extrapolated to NG transmissions and/or adverse health outcomes averted, our results would be an underestimate. Finally, previous studies have found discordant genotypes at different anatomic sites.[23] We assume that patients with discordant results will be treated with dual therapy, which is reflected in the lower range of ciprofloxacin susceptibility. It is important to note that our model is flexible and can be adjusted with parameters specific to a region or facility.

In conclusion, our cost minimization analysis found that the costs of providing *gyr*A testing for asymptomatic patients diagnosed as having NG would be offset by treatment savings when the cost of the test was $50. At a cost less than $50, the assay would result in cost savings. In scenarios where the ciprofloxacin susceptibility level was high, adding the *gyr*A NG susceptibility assay at a cost up to $114 would still result in overall cost neutrality. Thus, adding *gyr*A testing to sexually transmitted disease screening could yield savings to the health care system and potentially help address the rising threat of NG antimicrobial resistance.

REFERENCES

1. World Health Organization. International organizations unite on critical recommendations to combat drug-resistant infections and prevent staggering number of deaths each year. Available at: https://www.who.int/news-room/detail/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis. Accessed October 19, 2019.
2. UN Interagency Coordination Group on Antimicrobial Resistance. No time to wait: Securing the future from drug-resistant infections. Available at: https://www.who.int/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdf?sfvrsn=5b424d7_6. Accessed October 18, 2019.
3. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance report 2017. Available at: https://www.cdc.gov/std/stats17/2017-STD-Surveillance-Report_CDC-clearance-9.10.18.pdf. Accessed October 18, 2019.
4. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med 2012; 366:485–487.
5. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Available at: http://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed October 18, 2019.
6. Davies SC, Fowler T, Watson J, et al. Annual report of the chief medical officer: Infection and the rise of antimicrobial resistance. Lancet 2013; 381:1606–1609.
7. Kirkcaldy RD, Weinstock HS, Moore PC, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. Clin Infect Dis 2014; 59: 1083–1091.
8. Taylor SN, Marrazzo J, Batteiger BE, et al. Single-dose zoliflodacin (ETX0914) for treatment of urogenital gonorrhea. N Engl J Med 2018; 379:1835–1845.
9. Campos-Outcalt D. CDC update on gonorrhea: expand treatment to limit resistance. J FAM PRACT 2011; 60:736–740.
10. Centers for Disease Control and Prevention. Cephalosporin-resistant *Neisseria gonorrhoeae* public health response plan. Available at: https://www.cdc.gov/std/treatment/ceph-r-responseplanjuly30-2012.pdf. Accessed October 18, 2019.
11. Fingerhuth SM, Bonhoeffer S, Low N, et al. Antibiotic-resistant *Neisseria gonorrhoeae* spread faster with more treatment, not more sexual partners. PLoS Pathog 2016; 12:e1005611.
12. Allan-Blitz LT, Wang X, Klausner JD. Wild-type gyrase A genotype of *Neisseria gonorrhoeae* predicts in vitro susceptibility to ciprofloxacin: A systematic review of the literature and meta-analysis. Sex Transm Dis 2017; 44:261–265.
13. Allan-Blitz LT, Hemarajata P, Humphries RM, et al. Ciprofloxacin may be efficacious in treating wild-type gyrase A genotype *Neisseria gonorrhoeae* infections. Sex Transm Dis 2018; 45:e18.
14. Klausner JD, Kerndt P. Cephalosporin resistance in *Neisseria gonorrhoeae* infections. JAMA 2013; 309:1989.
15. Gaydos CA, Van Der Pol B, Jett-Goheen M, et al. Performance of the Cepheid CT/NG Xpert rapid PCR test for detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. J Clin Microbiol 2013; 51: 1666–1672.
16. Centers for Medicare and Medicaid Services. National Average Drug Acquisition Cost (NADAC). Available at: https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d/data. Accessed October 18, 2019.
17. Centers for Medicare and Medicaid Services. Centers for Medicare and Medicaid Services (CMS) physician fee schedule. (HCPCS 96372). Available at: https://www.cms.gov/apps/physician-fee-schedule/search/search-results.aspx?Y=0&T=0&HT=0&CT=0&H1=99213&M=5. Accessed October 18, 2019.
18. Chesson HW, Kirkcaldy RD, Gift TL, et al. Ciprofloxacin resistance and gonorrhea incidence rates in 17 cities, United States, 1991–2006. Emerg Infect Dis 2014; 20:612–619.
19. Chan CH, McCabe CJ, Fisman DN. Core groups, antimicrobial resistance and rebound in gonorrhoea in North America. Sex Transm Infect 2012; 88:200–204.
20. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: Implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr 2000; 24:48–56.
21. Chesson HW, Collins D, Koski K. Formulas for estimating the costs averted by sexually transmitted infection (STI) prevention programs in the United States. Cost Eff Resour Alloc 2008; 6:10.
22. Chesson HW, Kirkcaldy RD, Gift TL, et al. An illustration of the potential health and economic benefits of combating antibiotic-resistant gonorrhea. Sex Transm Dis 2018; 45:250–253.
23. Allan-Blitz LT, Ellis OL, Bolan R, et al. The frequency of discordant gyrase A genotypes among cases of multiple neisseria gonorrhoeae infections at different anatomic sites. Sex Transm Dis 2019; 46:e3–e4.