A Cost Analysis of Gyrase A Testing and Targeted Ciprofloxacin Therapy Versus Recommended 2-Drug Therapy for *Neisseria gonorrhoeae* Infection

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Background: Novel approaches to combating drug-resistant *Neisseria gonorrhoeae* infections are urgently needed. Targeted therapy with ciprofloxacin has been made possible by a rapid assay for genotyping the gyrase A (*gyr*A) gene; a nonmutated gene reliably predicts susceptibility to ciprofloxacin.

Methods: We determined the costs of running the *gyr*A assay, 500 mg of ciprofloxacin, 250 mg of ceftriaxone injection, and 1000 mg of azithromycin. Cost estimates for *gyr*A testing included assay reagents and labor. Cost estimates for ceftriaxone included medication, injection, administration, supplies, and equipment. We measured the cost of using the *gyr*A assay and treatment based on genotype using previously collected data over a 13-month period between November 2015 and November 2016 for all *N. gonorrhoeae* cases diagnosed at UCLA. We subsequently developed 3 cost models, varying the frequency of testing and prevalence of *N. gonorrhoeae* infections with ciprofloxacin-resistant or genotype-indeterminate results. We compared those estimates with the cost of recommended 2-drug therapy (ceftriaxone and azithromycin).

Results: Based on a 65.3% prevalence of cases with ciprofloxacin-resistant or genotype indeterminate *N. gonorrhoeae* infections when running an average of 1.7 tests per day, the per-case cost of *gyr*A genotyping and targeted therapy was US $197.19. The per-case cost was US $155.16 assuming a 52.6% prevalence of ciprofloxacin-resistant or genotype-indeterminate infections when running an average of 17 tests per day. The per-case cost of 2-drug therapy was US $142.75.

Conclusions: Direct costs of *gyr*A genotyping and targeted ciprofloxacin therapy depend on the prevalence of ciprofloxacin-resistant or genotype-indeterminate infections and testing frequency.

Neisseria gonorrhoeae is the cause of one of the most common bacterial sexually transmitted infections in the United States[1] and has developed resistance to all antimicrobials used for treatment.[2] In 2013, the Centers for Disease Control and Prevention declared multidrug-resistant *N. gonorrhoeae* to be 1 of 3 urgent antibiotic-resistant threats to public health.[3] In response to that threat, various strategies for combating resistance have emerged.[4]

One strategy calls for the targeted use of antibiotics previously thought ineffective,[5,6] which has been made possible by the development of rapid molecular assays for the prediction of antibiotic susceptibility.[7] One of those assays, which detects mutation at codon 91 of the gyrase A (*gyr*A) gene of *N. gonorrhoeae* has been extensively studied, and a nonmutated genotype has been shown to reliably predict susceptibility to ciprofloxacin.[8] Furthermore, since November 2015, that genotypic assay has been implemented into routine clinical practice at the University of California, Los Angeles Health System and has been shown to influence the treatment selection among patients not treated on the same day as specimen collection.[9]

A recent modeling study concluded that treatment may be a major driver of resistance in *N. gonorrhoeae,*[10] therefore, use of ciprofloxacin instead of ceftriaxone in susceptible infections may reduce the selective pressure for and thus the emergence of ceftriaxone resistance.[5] The utility of that approach is predicated on a high prevalence of *N. gonorrhoeae* infections that are susceptible to ciprofloxacin. Fortunately, approximately 80% of *N. gonorrhoeae* infections in the United States are susceptible to ciprofloxacin; however, susceptibility varies by subgroup (men who have sex with men vs heterosexual men, eastern United States vs Western United States, etc.).[1] An additional consideration is the cost of implementing the genotypic assay, which has not previously been estimated. A cost estimate will be useful in consideration of the cost-effectiveness of implementation of the *gyr*A assay. Here, we compared the actual costs of an ongoing program for *gyr*A genotyping and targeted ciprofloxacin therapy at the University of California, Los Angeles over a 13-month period with the costs of recommended 2-drug ceftriaxone and azithromycin therapy. We also modeled the costs by varying the prevalence of ciprofloxacin-resistant *N. gonorrhoeae* infections, indeterminate genotype results, and the number of tests run per day.

METHODS

*Gyr*A Assay Implementation at University of California, Los Angeles

Data were retrospectively collected on all laboratory-confirmed cases of *N. gonorrhoeae* infection at the University of California, Los Angeles Health System over a 13-month study period between November 1, 2015, and November 30, 2016. That health system contains 2 hospitals, 2 emergency departments, and over 150 primary care clinics serving approximately 500,000 patient-visits each year. Data were collected on the number of cases of *N. gonorrhoeae* infection, date of specimen collection, date of treatment, treatment selection, and *gyr*A genotype results. All infections were detected by the Cobas 4800 CT/NG assay (Roche

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Molecular Systems, Pleasanton, Calif). All *N. gonorrhoeae*-positive specimens were reflexed to the real-time polymerase chain reaction (PCR) *gyr*A genotypic assay, coupled with high-resolution melt analysis using fluorescence resonance energy transfer probes that target the *gyr*A gene.[11] Infections from individual anatomic sites (rectal, pharyngeal, urethral, vaginal, cervical) were treated as unique infections, whereas a single patient with multiple infections on 1 date was considered a case. Wild-type infections were defined as the most common gene sequence; the most common gene sequence is associated with ciprofloxacin susceptibility.[8]

Costs

We determined the per-case cost of an ongoing *N. gonorrhoeae* resistance screening program at the University of California, Los Angeles, which included screening using the *gyr*A assay, and targeted therapy based on genotype results with either ciprofloxacin 500 mg orally for cases with only wild-type genotype infections or recommended 2-drug therapy (ceftriaxone, 250 mg injection and azithromycin, 1000 mg orally) for cases in which any infection had either a mutant or indeterminate genotype result. Given that some cases present with multiple infections and thus the cost of multiple genotypic tests will be incurred, we determined the average number of tests per case and applied that to our cost estimates. Cases with discordant genotype results among multiple infections were treated as mutant if any infection had either an indeterminate or mutant genotype. The financial costs of using the *gyr*A genotypic assay included per-specimen expenditures on personnel (eg, laboratory technicians) and supplies (reagents, medications). We also included the cost of recommended 2-drug therapy among ciprofloxacin-resistant infections or infections with indeterminate genotype results. The per-treatment costs for recommended 2-drug therapy included expenditures on personnel (eg, injection of ceftriaxone by medical assistants) and supplies (eg, medications, syringe, and needle). We also included the overhead cost of clinic space for 2-drug therapy, because a second visit is required for patients not treated on the same day as specimen collection. We did not include the costs of the initial clinic visit, because that cost would be the same regardless of treatment strategy. The cost of empiric azithromycin therapy for *Chlamydia trachomatis* infection was not included in the costs of targeted therapy assuming a negative *C. trachomatis* nucleic acid amplification test; however, we did add the cost of azithromycin 1000 mg for coinfection with *C. trachomatis* among those not receiving dual therapy, assuming a prevalence of coinfection of 40%.[12]

We then developed 3 cost models by varying the frequency of testing, the prevalence of ciprofloxacin-resistant *N. gonorrhoeae* infections, and the prevalence of indeterminate genotype results. We determined the average number of tests per day by summing the percentage of days on which x number of tests were performed, only including days on which testing actually occurred. Model 1 multiplied by 10 the average number of tests per day. Models 2A and 2B used the national estimate of the prevalence of ciprofloxacin-resistant *N. gonorrhoeae* infections of 22.3%.[1] Model 2A used the actual average number of tests run per day, whereas model 2B multiplied by 10 the average number of tests per day. Model 3 used a 15% prevalence of infections with an indeterminate genotype, which is approximately one half of the prevalence reported in this study and in previous studies using the *gyr*A assay.[11,13] We then compared all cost models using the genotypic assay with the financial costs of recommended 2-drug therapy for all infections.

Importantly, because actual costs were of an ongoing testing program, we did not include start-up costs of machine procurement or training. Furthermore, because we were focused on direct testing and treatment costs with the hope of informing future implementation of the *gyr*A assay at other laboratories, we did not include patient costs, such as the cost to the patient of returning to clinic for ceftriaxone injection versus picking up ciprofloxacin from a pharmacy.

Personnel time and salaries, as well as the cost of supplies, were determined by interviews with laboratory personnel and experts in the field. For further validation, we timed the duration of the genotypic assay, which was in agreement with the costs provided by the laboratory personnel. The costs of the antibiotics were based on published data[14] and interviews with clinic managers (Table 1).

All costs are expressed in 2016 United States dollars. Inflation was accounted for using the medical care items consumer price indices for all urban consumers (CPI-U) and the following formula: cost in reported year × CPI-U (for base year)/CPI-U (for reported year).

RESULTS

Over the 13-month study period, there were 285 anatomic site-specific *N. gonorrhoeae* infections with *gyr*A genotype results among 234 cases. Of those 285 infections, 113 (39.6%) were wild-type (nonmutated), 88 (30.9%) were mutant, and 84 (29.5%) were indeterminate. Fourteen of the cases with wild-type infections had additional infections with either indeterminate or mutant genotype results on the same date. Thus, of the 234 unique cases with genotype results, the per-case prevalence of genotype was 81 (34.7%) wild-type, 82 (35.0%) mutant, and 71 (30.3%) indeterminate genotype.

Based on the 234 unique cases in 13 months, we estimated that there would be 216 unique cases per year. We found that on 54.8% of days on which testing occurred, only 1 test was run, whereas 2 tests were run on 26.5% of days, 3 tests were run on 12.7% of days, 4 tests were run on 3.6% of days, 5 tests were

TABLE 1. The Costs of Gryase A Genotyping, Ciprofloxacin, Ceftriaxone, and Azithromycin

Items	Average Cost US $	References
Gyrase A assay individual test		
PCR reagents	32.99	Interview with Laboratory Personnel
1-hour of Labor	49.42	Interview with Laboratory Personnel
Treatment		
Ciprofloxacin 500 mg*	2.44	Treatment Guidelines. The Medical Letter, 2013
Ceftriaxone Administration (injection, needle, syringe)	104.76	Interview with Clinic Manager
Ceftriaxone 250 mg*	19.24	Treatment Guidelines. The Medical Letter, 2013
Azithromycin 1000 mg*	18.75	Treatment Guidelines. The Medical Letter, 2013

All costs are expressed in 2016 United States dollars.

* Cost estimates from 2013 were adjusted for inflation using the medical care items consumer price indices for all urban consumers.

run on 1.8% of days, and 7 tests were run on 0.6% of days, averaging to 1.74 tests per day.

Each day of testing required 4 control reagents, equating to approximately US $40.00 daily plus the cost of the testing reagents (approximately US $10 per test). Other costs included approximately 1 hour per day of personnel time (including assay preparation, results interpretation, and reporting), which equated to an additional US $49.42 per test per run (Table 1). The per-test cost of running the *gyr*A assay when an average of 1.74 tests were run per day was therefore US $82.40 per specimen; however, we found that an average of 1.22 tests were run for any given case. Thus, the per-case estimate of cost of the *gyr*A assay was US $100.53. The per-case cost of the *gyr*A assay when an average of 17 tests were run per day was US $75.36, again assuming an average of 1.22 tests per case.

The cost of ciprofloxacin was US $2.44 per pill. The cost of 2-drug therapy included the cost of 1000 mg of azithromycin, which was US $18.75 for two 500-mg tablets, and $124.00 per injection for 250 mg of ceftriaxone, needle, syringe, and labor of injection. The cost of 2-drug therapy with ceftriaxone and azithromycin was US $142.75 per treatment.

To be conservative, we assumed that all cases with indeterminate genotypes would be treated with 2-drug therapy, thus 65.3% of infections subjected to *gyr*A genotyping will incur costs of 2-drug therapy as well as the costs of genotyping. The average cost of 2-drug therapy among those with resistant or indeterminate infections would be US $93.21 per case. An additional average cost of US $0.84 per case for ciprofloxacin among the 34.7% of infections with a wild-type *gyr*A genotype would be incurred, as well as a cost of US $2.60 for azithromycin to treat coinfection with *C. trachomatis* among 40.0% of those with wild-type infections. Thus, the cost of targeted therapy, including 2-drug therapy among those with resistant or indeterminate infections at a prevalence of 65.3%, and when running an average of 1.74 tests per day was US $197.19 per case. The cost difference between the 2 approaches in that scenario was US $54.44 (Table 2).

The cost of targeted therapy assuming a 65.3% prevalence of ciprofloxacin-resistant or -indeterminate infections when running an average of 17 tests per day was US $172.02 per case. The cost difference between that and the 2-drug therapy was US $29.27. Assuming a 22.3% prevalence of ciprofloxacin-resistant *N. gonorrhoeae* infections, and 30.3% prevalence of infections with an genotype indeterminate genotype result, the cost of targeted therapy when running an average of 1.74 tests per day was US $180.33 per case. The cost difference between the 2 approaches in that scenario was US $37.57. Assuming the same 52.6% prevalence of either mutant or genotype indeterminate infections, when running an average of 17 tests per day the total cost was US $155.16 per case, and the cost difference was US $12.41. Finally, when running an average of 1.74 tests per day and assuming a 35.0% prevalence of ciprofloxacin-resistant infections and a 15.0% prevalence of infections with an indeterminate *gyr*A genotype, the per-case cost was US $176.87. The cost difference in that scenario was US $34.12.

DISCUSSION

We determined the cost of using a rapid genotypic *gyr*A assay for the promotion of targeted ciprofloxacin therapy for *N. gonorrhoeae* infections. Currently, the direct costs of targeted therapy vary by frequency of testing, prevalence of ciprofloxacin resistance, and prevalence of infections with an indeterminate genotype. Our results accounting for 4 different scenarios demonstrated a range of per case cost differences (US $12.41–54.44) between targeted therapy and 2-drug therapy. However, those cost differences may be an overestimate given that the cost of 2-drug therapy extends beyond direct costs. Indirect costs and unquantified benefits must be considered as well.

TABLE 2. A Comparison of the Per-Case Cost of *gyr*A Genotype Testing and Targeted Ciprofloxacin Therapy for *Neisseria gonorrhoeae* Versus Recommended 2-Drug Therapy in 4 Different Scenarios

	Cost Incurred for 2-Drug Therapy		Cost Incurred for Coinfection	Cost Incurred for Targeted Therapy		Cost Analysis	
Treatment strategies	**Cost of Ceftriaxone**	**Cost of Azithromycin**	**Cost of Azithromycin**	**Cost of Ciprofloxacin**	**Cost of Assay**	**Cost Per Case**	**Cost Difference**
2-Drug strategy	$124.00	$18.75	N/A	N/A	N/A	$142.75	-
Targeted strategy							
Actual*	$80.97	$12.24	$2.60	$0.85	$100.53	$197.19	$54.44
Model 1†	$80.97	$12.24	$2.60	$0.85	$75.36	$172.02	$29.27
Model 2A‡	$65.22	$9.86	$3.56	$1.16	$100.53	$180.33	$37.57
Model 2B§	$65.22	$9.86	$3.56	$1.16	$75.36	$155.16	$12.41
Model 3¶	$62.00	$9.38	$3.75	$1.22	$100.53	$176.87	$34.12

Prevalence of coinfection with *C. trachomatis* assumed to be 40.0%.

The cost difference is the difference between the per-case cost of 2-drug therapy and the per-case cost of targeted therapy.

All costs are expressed in 2016 United States dollars.

The costs of 2-drug therapy were incurred by every individual in the "2-drug strategy" group, as well as by those in the 'targeted strategy' group whose *Neisseria gonorrhoeae* genotype test result indicated ciprofloxacin resistance or was indeterminate.

* Calculated assuming 1.74 tests per day, a 35.0% prevalence of cases with ciprofloxacin-resistant *Neisseria gonorrhoeae* infections, and a 30.3% prevalence of an indeterminate genotype result.

† Calculated assuming 17 tests per day, a 35.0% prevalence of cases with ciprofloxacin-resistant *Neisseria gonorrhoeae* infections, and a 30.3% prevalence of an indeterminate genotype result.

‡ Calculated assuming 1.74 tests per day, a 22.3% prevalence of cases with ciprofloxacin-resistant *Neisseria gonorrhoeae* infections, and a 30.3% prevalence of an indeterminate genotype result.

§ Calculated assuming 17 tests per day, a 22.3% prevalence of cases with ciprofloxacin-resistant *Neisseria gonorrhoeae* infections, and a 30.3% prevalence of an indeterminate genotype result.

¶ Calculated assuming 1.74 tests per day, a 35.0% prevalence of cases with ciprofloxacin-resistant *Neisseria gonorrhoeae* infections, and a 15.0% prevalence of an indeterminate genotype result.

One additional societal cost of 2-drug therapy is the potential promotion of antimicrobial resistance by overtreatment with ceftriaxone.[10] Thus, targeted therapy with ciprofloxacin may reduce the costs associated with the emergence of multidrug-resistant *N. gonorrhoeae* infections. Similarly, given the increasing prevalence of ceftriaxone-resistant *N. gonorrhoeae*, the prevalence and costs of pelvic inflammatory disease, infertility, and other long-term sequelae of inadequately treated infections might rise concomitantly. Finally, previous studies have demonstrated an increased risk for the transmission and acquisition of HIV infection among patients with *N. gonorrhoeae* infections.[15–18] Therefore, the overall costs of continuing to treat *N. gonorrhoeae* infections with the 2-drug regimen are likely higher than estimated here. Future cost-effectiveness studies may benefit from including some of those indirect costs we were unable to include.

Beyond cost, there may be further unquantified benefits to targeted therapy. One such benefit may be a reduction in patient discomfort or risk of needle-stick injury resulting from a reduction in ceftriaxone injections. Electronic prescription of ciprofloxacin without the requirement of a clinic visit to receive a ceftriaxone injection may improve the proportion of patients and partners treated and reduce the time to treatment. Partner treatment outcomes may also be improved as a result of the use of oral therapy as opposed to injectable therapy. However, there may also be treatment delays with routine reflex *gyr*A testing, thus close monitoring will be necessary after any implementation.

The importance of reflex *gyr*A testing is further supported by a recent modeling study, which concluded that the use of point-of-care resistance assays, such as the *gyr*A assay, can slow the emergence of single-drug antimicrobial resistance when used in at least 10% of the population.[19] Interestingly, however, that same study predicted that single-drug point-of-care tests will not impact the emergence of triple antibiotic-resistant strains, something which multidrug resistance assays can delay.[19] There are other mutations that can predict *N. gonorrhoeae* susceptibility to antibiotics, such as alterations in the *pen*A gene and mosaic insertion sequences[20]; thus, future studies should evaluate the cost of implementing multiple resistance assays.

Beyond the guidance of antimicrobial therapy, reflex *gyr*A genotyping of *N. gonorrhoeae* infections may be useful for surveillance purposes. The Gonococcal Isolates Surveillance Program is currently the standard for *N. gonorrhoeae* antimicrobial resistance monitoring in the United States; however, that program uses minimum inhibitory concentration values for the determination of antimicrobial susceptibility,[21] which is dependent on *N. gonorrhoeae* culture. In clinical practice, culture has largely been replaced by nucleic acid amplification testing for the diagnosis of *N. gonorrhoeae* infection, despite such testing not providing data on antimicrobial susceptibility. In addition, the population monitored by the Gonococcal Isolates Surveillance Program may not be representative of the general population. Thus, implementing routine *gyr*A reflex testing[22] may improve the overall surveillance of ciprofloxacin-resistant *N. gonorrhoeae* infections in the United States. Importantly, a separate cost analysis would need to be conducted to evaluate the expenses and benefits of using *gyr*A genotyping for surveillance purposes.

Ciprofloxacin has been shown to be greater than 99% effective for the treatment of phenotypically susceptible *N. gonorrhoeae* infections[23]; however, a valid concern is the lack of clinical studies comparing treatment outcomes between patients with wild-type infections treated with ciprofloxacin and those treated with recommended 2-drug therapy. A clinical trial is currently underway to evaluate outcomes among patients with wild-type *gyr*A *N. gonorrhoeae* infection treated with single-dose ciprofloxacin 500 mg orally.[24]

The cost estimates of personnel and supplies for *gyr*A genotype testing, which included the cost of reagents, may vary in other laboratories. We did not include the cost of office space for recommended 2-drug therapy in our final cost models given the variation among clinics, counties, and states. There was no facility charge at the clinic where we interviewed the clinic manager, but the average cost of class A office space in Los Angeles county was US $41.13 per-ft^2/year.[25] Thus, the cost of 2-drug therapy, which requires patients to return to clinic to receive ceftriaxone injection, may be higher than was calculated here.

Additional considerations for laboratories include the Centers for Medicare and Medicaid Services reimbursement for the assay as well as the varying wages of laboratory personnel across the different states. Reimbursement in California for similar molecular assays including those for methicillin-resistant *Staphylococcus aureus* and GeneXpert for multidrug-resistant *Mycobacterium tuberculosis* is approximately US $48.00 according to the Centers for Medicare and Medicaid Services 2017 Clinical Diagnostic Laboratory Fee Schedule,[26] which would not cover the current per test costs of the *gyr*A assay in our program. In laboratories where *gyr*A testing would be performed more frequently than 2 tests per day, however, the cost of targeted therapy may be reduced, because the fixed costs of 4 controls per day would contribute less relative to the overall costs. Additionally, wages for laboratory personnel in California are also among the highest in the country.[27] Given those 2 considerations, the cost of targeted therapy calculated here might not be generalizable to other laboratories. However, using local values and the same cost structure we presented here, other programs may be able to compute an approximate cost of targeted therapy, which will help guide decisions about further implementation of the *gyr*A assay.

Limitations

Our study has several limitations. Primarily, it is difficult to account for all of the inherent costs in both screening and treatment. Importantly, we were unable to include costs of maintenance or repairs for the PCR machine used for *gyr*A genotyping, thus our results may slightly underestimate the cost of targeted therapy. Furthermore, because we were interested in the costs of an already established testing program, our estimates are applicable only to laboratories that currently have the necessary instruments. On the other hand, because we did not exclude those treated on the same day as specimen collection—which may be as high as 40% in some settings[9]—our results may overestimate the cost of targeted therapy by including the cost of genotyping among cases that had already been treated. Additionally, our sample size was small, limiting the precision of our findings, and therefore further research is necessary. However, our aim was to provide the costs of the *gyr*A testing program at UCLA with the hope of informing the implementation of *gyr*A testing at other programs, thus we feel that those limitations do not negate the importance of our findings.

CONCLUSIONS

Our findings provide a cost of routine *gyr*A genotype testing and targeted therapy for *N. gonorrhoeae* infections with estimated costs for additional modeled scenarios. The direct costs of targeted ciprofloxacin vary according to the prevalence of ciprofloxacin resistant infections, the frequency of genotype testing, and the prevalence of infections with indeterminate genotype results. Further research is needed to look at the effectiveness of using the *gyr*A assay and targeted ciprofloxacin therapy on the prevalence of antimicrobial resistance.

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