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A Cost Analysis of Gyrase A Testing and Targeted Ciprofloxacin Therapy vs. Recommended Two-Drug Therapy for *Neisseria gonorrhoeae* Infection

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Abstract

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 non-mutated gene reliably predicts susceptibility to ciprofloxacin.

Methods—We determined the costs of running the *gyr*A assay, 500 mg of ciprofloxacin, 250 mg ceftriaxone injection and 1000 mg 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 thirteen-month period between November 2015 - November 2016 for all *Neisseria gonorrhoeae* cases diagnosed at UCLA. We subsequently developed three cost models, varying the frequency of testing and prevalence of *Neisseria gonorrhoeae* infections with ciprofloxacin resistant or genotype indeterminate results. We compared those estimates with the cost of recommended two-drug therapy (ceftriaxone and azithromycin).

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

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infections when running an average of 17 tests per day. The per-case cost of two-drug therapy was $142.75.

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

Summary:

The costs of using a genotypic assay for Neisseria gonorrhoeae susceptibility testing and targeted therapy were dependent on the frequency of testing, prevalence of ciprofloxacin resistance, and assay performance.

Introduction

Neisseria gonorrhoeae is the cause of one of the most common bacterial sexually transmitted infections (STIs) 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 *Neisseria gonorrhoeae* to be one of three 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 *Neisseria gonorrhoeae* has been extensively studied, and a non-mutated 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 *Neisseria 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 *Neisseria gonorrhoeae* infections that are susceptible to ciprofloxacin. Fortunately, approximately 80% of *Neisseria gonorrhoeae* infections in the United States are susceptible to ciprofloxacin, however susceptibility varies by sub-group (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 thirteen-month period with the costs of recommended two-drug ceftriaxone and azithromycin therapy. We also modeled the costs by varying the prevalence of ciprofloxacin resistant *Neisseria 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 *Neisseria gonorrhoeae* infection at the University of California, Los Angeles Health System over a thirteen-month study period between November 1st 2015 and November 30th 2016. That health system contains two hospitals, two 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 *Neisseria 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 Molecular Systems, Pleasanton, CA, USA). All *Neisseria gonorrhoeae*-positive specimens were reflexed to the real-time 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, while a single patient with multiple infections on one 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 *Neisseria 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 two-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 utilizing the *gyr*A genotypic assay included per-specimen expenditures on personnel (e.g. laboratory technicians), and supplies (reagents, medications). We also included the cost of recommended two-drug therapy among ciprofloxacin resistant infections or infections with indeterminate genotype results. The per-treatment costs for recommended two-drug therapy included expenditures on personnel (e.g. injection of ceftriaxone by medical assistants), and supplies (e.g. medications, syringe, and needle). We also included the overhead cost of clinic space for two-drug therapy, as 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, as 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 *Chlamydia trachomatis* nucleic acid amplification test; however, we did add the cost of azithromycin 1000 mg for co-infection with *Chlamydia trachomatis* among those not receiving dual therapy, assuming a prevalence of co-infection of 40% (12).

We then developed three cost models by varying the frequency of testing, the prevalence of ciprofloxacin resistant *Neisseria 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 *Neisseria gonorrhoeae* infections of 22.3% (1). Model 2A used the actual average number of tests run per day, while 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 prior studies using the *gyr*A assay (11, 13). We then compared all cost models using the genotypic assay with the financial costs of recommended two-drug therapy for all infections.

Importantly, since actual costs were of an ongoing testing program, we did not include start-up costs of machine procurement or training. Furthermore, as 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 vs. 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) (15) and the following formula: Cost in reported year x CPI-U (for base year) / CPI-U (for reported year).

Results

Over the thirteen-month study period, there were 285 anatomic site-specific *Neisseria gonorrhoeae* infections with *gyr*A genotype results among 234 cases. Of those 285 infections, 113 (39.6%) were wild-type (non-mutated), 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 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, while 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 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 four control reagents, equating to approximately $40.00 daily plus the cost of the testing reagents (approximately $10 per test). Other costs included

approximately one hour per day of personnel time (including assay preparation, results interpretation and reporting), which equated to an additional $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 $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 $100.53. The per-case cost of the *gyr*A assay when an average of 17 tests were run per day was $75.36, again assuming an average of 1.22 tests per case.

The cost of ciprofloxacin was $2.44 per pill. The cost of two-drug therapy included the cost of 1000 mg of azithromycin, which was $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 two-drug therapy with ceftriaxone and azithromycin was $142.75 per treatment.

To be conservative, we assumed that all cases with indeterminate genotypes would be treated with two-drug therapy, thus 65.3% of infections subjected to *gyr*A genotyping will incur costs of two-drug therapy as well as the costs of genotyping. The average cost of two-drug therapy among those with resistant or indeterminate infections would be $93.21 per case. An additional average cost of $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 $2.60 for azithromycin to treat co-infection with *Chlamydia trachomatis* among 40.0% of those with wild-type infections. Thus, the cost of targeted therapy, including two-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 $197.19 per case. The cost difference between the two approaches in that scenario was $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 $172.02 per case. The cost difference between that and two-drug therapy was $29.27. Assuming a 22.3% prevalence of ciprofloxacin resistant *Neisseria gonorrhoeae* infections, and 30.3% prevalence of infections with an indeterminate genotype result, the cost of targeted therapy when running an average of 1.74 tests per day was $180.33 per case. The cost difference between the two approaches in that scenario was $37.57. Assuming the same 52.6% prevalence of either mutant or indeterminate infections, when running an average of 17 tests per day the total cost was $155.16 per case, and the cost difference was $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 $176.87. The cost difference in that scenario was $34.12.

Discussion

We determined the cost of utilizing a rapid genotypic *gyr*A assay for the promotion of targeted ciprofloxacin therapy for *Neisseria 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 four different scenarios demonstrated a range of per case cost differences ($12.41 - $54.44)

between targeted therapy and two-drug therapy. However, those cost differences may be an over-estimate given that the cost of two-drug therapy extends beyond direct costs. Indirect costs and un-quantified benefits must be considered as well.

One additional societal cost of two-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 *Neisseria gonorrhoeae* infections. Similarly, given the increasing prevalence of ceftriaxone resistant *Neisseria 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 *Neisseria gonorrhoeae* infections (16–19). Therefore, the overall costs of continuing to treat *Neisseria gonorrhoeae* infections with the two-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 un-quantified 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 (20). 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 (20). There are other mutations that can predict *Neisseria gonorrhoeae* susceptibility to antibiotics, such as alterations in the *pen*A gene and mosaic insertion sequences (21), thus future studies should evaluate the cost of implementing multiple resistance assays.

Beyond the guidance of antimicrobial therapy, reflex *gyr*A genotyping of *Neisseria gonorrhoeae* infections may be useful for surveillance purposes. The Gonococcal Isolates Surveillance Program is currently the standard for *Neisseria gonorrhoeae* antimicrobial resistance monitoring in the United States; however, that program uses minimum inhibitory concentration values for the determination of antimicrobial susceptibility (22), which is dependent on culture. In clinical practice, culture has largely been replaced by nucleic acid amplification testing for the diagnosis of *Neisseria 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 (23) may improve the overall surveillance of ciprofloxacin resistant *Neisseria 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 >99% effective for the treatment of phenotypically susceptible *Neisseria gonorrhoeae* infections (24), 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 two-drug therapy. A clinical trial is currently underway to evaluate outcomes among patients with wild-type *gyr*A *Neisseria gonorrhoeae* infection treated with single-dose ciprofloxacin 500 mg orally (25).

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 two-drug therapy in our final cost 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 $41.13 per-square-foot/year (26). Thus, the cost of two-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 (CMS) 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 *Staphlococcus aureus* and GeneXpert® for multidrug-resistant *Mycobacterium tuberculosis* is approximately $48.00 according to the CMS 2017 Clinical Diagnostic Laboratory Fee Schedule (27), 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 two tests per day, however, the cost of targeted therapy may be reduced, as the fixed costs of four 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 (28). Given those two 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, as 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.

Conclusion

Our findings provide a cost of routine *gyr*A genotype testing and targeted therapy for *Neisseria gonorrhoeae* infections with estimated costs for additional modeled scenarios. The direct costs of targeted ciprofloxacin vary according to the prevalence of 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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Table 1:

The costs of gryase A genotyping, ciprofloxacin, ceftriaxone, and azithromycin.

Item	Average Cost Per Test (USD)	Reference
Gyrase A Assay		
PCR Reagents	$32.99	Interview with Laboratory Personnel
Labor	$49.42	Interview with Laboratory Personnel
Treatment		
Ciprofloxacin *	$ 2.44	Treatment Guidelines. The Medical Letter®, 2013
Ceftriaxone 250 mg (medication, injection, needle, syringe)	$124.00	Interview with Clinic Manager
Azithromycin *	$18.75	Treatment Guidelines. The Medical Letter®, 2013

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

• All costs are expressed in 2016 United States dollars

Table 2:

A comparison of the per-case cost of *gyr*A genotype testing and targeted ciprofloxacin therapy for *Neisseria gonorrhoeae* vs. recommended two-drug therapy in four different scenarios

	Cost Incurred for Two-Drug Therapy		Cost Incurred for Co-Infection	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**
Two-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	
Model 1 †	$80.97	$12.24	$2.60	$0.85	$75.36	$172.02	
Model 2A §	$65.22	$9.86	$3.56	$1.16	$100.53	$180.33	
Model 2B π	$65.22	$9.86	$3.56	$1.16	$75.36	$155.16	
Model 3 ¢	$62.00	$9.38	$3.75	$1.22	$100.53	$176.87	

* 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

π 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

• Prevalence of co-infection with *Chlamydia trachomatis* assumed to be 40.0%

• The cost difference is the difference between the per-case cost of two-drug therapy and the per-case cost of targeted therapy

• All costs are expressed in 2016 United States dollars

• The costs of two-drug therapy were incurred by every individual in the ‘two-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