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https://escholarship.org/uc/item/1dp7453n

Journal

Clinical Infectious Diseases, 73(2)

ISSN

1058-4838

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Publication Date

2021-07-15

DOI

10.1093/cid/ciaa596

Peer reviewed

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Clinical Infectious Diseases

MAJOR ARTICLE

Resistance-Guided Treatment of Gonorrhea: A Prospective Clinical Study

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(See the Editorial Commentary by Marks and Harding-Esch on pages 304–5.)

Background. Novel treatment strategies to slow the continued emergence and spread of antimicrobial resistance in *Neisseria gonorrhoeae* are urgently needed. A molecular assay that predicts in vitro ciprofloxacin susceptibility is now available but has not been systematically studied in human infections.

Methods. Using a genotypic polymerase chain reaction assay to determine the status of the *N. gonorrhoeae* gyrase subunit A serine 91 codon, we conducted a multisite prospective clinical study of the efficacy of a single oral dose of ciprofloxacin 500 mg in patients with culture-positive gonorrhea. Follow-up specimens for culture were collected to determine microbiological cure 5–10 days post-treatment.

Results. Of the 106 subjects possessing culture-positive infections with wild-type *gyrA* serine *N. gonorrhoeae* genotype, the efficacy of single-dose oral ciprofloxacin treatment in the per-protocol population was 100% (95% 1-sided confidence interval, 97.5–100%).

Conclusions. Resistance-guided treatment of *N. gonorrhoeae* infections with single-dose oral ciprofloxacin was highly efficacious. The widespread introduction and scale-up of *gyrA* serine 91 genotyping in *N. gonorrhoeae* infections could have substantial medical and public health benefits in settings where the majority of gonococcal infections are ciprofloxacin susceptible.

Clinical Trials Registration. NCT02961751.

Keywords. *Neisseria gonorrhoeae*; ciprofloxacin; antimicrobial resistance; serine 91; gyrase A gene.

Increasing antimicrobial resistance is a public health emergency [1]. In many countries more than 5% of *Neisseria gonorrhoeae* are resistant to extended-spectrum cephalosporins, the last available class of effective antimicrobial therapy [2, 3]. The treatment of antimicrobial-resistant *N. gonorrhoeae* infections can result in clinical treatment failure, clinical complications, and the subsequent transmission of antimicrobial-resistant organisms [4, 5]. Resistance may actually be perpetuated by the frequent screening and treatment of those with *N. gonorrhoeae* infections [6, 7]. Reducing therapy with a single recommended class of antibiotics and treating with different efficacious classes of antibiotics might be a novel strategy to decrease the selection pressure for resistance and slow its continued emergence [8–10]. The US Centers for Disease Control and Prevention's (CDC's) current recommended therapy, ceftriaxone 250 mg plus azithromycin 1 g, requires an intramuscular injection, which can cause patient discomfort and often an additional clinical visit for administration [11]. An additional effective oral therapy would be highly advantageous. Oral therapy may also facilitate partner treatment and treatment in nonclinical settings [12].

Clinical evidence demonstrates that ciprofloxacin 500 mg, as an oral single-dose therapy, is highly efficacious for gonorrhea treatment in susceptible *N. gonorrhoeae* infections. In fact, ciprofloxacin was previously recommended by the CDC as first-line therapy until increasing ciprofloxacin resistance was noted [13]. Ciprofloxacin exerts its antibiotic effect through the binding of the bacterial DNA gyrase A subunit [14]. A single point mutation in the gyrase A gene (*gyrA*) that alters the DNA *gyrA* subunit is the main mechanism that renders ciprofloxacin ineffective in *N. gonorrhoeae* [15]. In a systematic review of 31 studies across 16 countries between 1996 and 2016 including over 5000 *N. gonorrhoeae* infections, we confirmed that the single point mutation in the serine 91 codon was highly predictive of almost all (>98.2%) ciprofloxacin resistance (ciprofloxacin minimum inhibitory concentration ≥1 μg/mL) in *N. gonorrhoeae* [16].

A small retrospective study suggested that the use of ciprofloxacin to treat wild-type *gyrA* serine 91 *N. gonorrhoeae* infections (ie, lacking any change in the serine 91 codon) was highly effective [17]. To determine the clinical efficacy of

Received 10 January 2020; editorial decision 14 April 2020; accepted 14 May 2020; published online 7 August 2020

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Clinical Infectious Diseases® 2021;73(2):298–303

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DOI: 10.1093/cid/ciaa596

ciprofloxacin 500 mg single-dose therapy in the treatment of *N. gonorrhoeae* wild-type *gyrA* serine 91 infections, we conducted a multisite prospective study of patients with culture-positive *N. gonorrhoeae*.

METHODS

Study Design

Our study was conducted from October 2016 through December 2018 at sexual health clinics in 7 cities in the United States (in San Diego, CA; San Francisco, CA; Los Angeles, CA; Washington, D.C.; Philadelphia, PA; Jackson, MS; New Orleans, LA). During the study period, all remnant *N. gonorrhoeae*–positive nucleic acid amplification test specimens from those clinics (Hologic Aptima Combo 2 assay for CT/NG [San Diego, CA] or Roche Cobas CT/NG [Pleasanton, CA]) were tested for the *N. gonorrhoeae* serine 91 *gyrA* genotype using a laboratory-developed polymerase chain reaction (PCR) test performed at 3 clinical microbiology laboratories at the University of California, Los Angeles; the San Francisco Department of Public Health; and the Philadelphia Department of Public Health [18]. In prior studies we found that assay to be in 100% concordance with agar dilution methods for detecting ciprofloxacin susceptibility [15]. Based on that serine 91 *gyrA N. gonorrhoeae* result at screening, study staff recruited untreated patients with wild-type *gyrA N. gonorrhoeae* infection. Consenting patients provided specimens from the anatomic site of their infection(s) (rectal, throat, and genital swabs) for gonococcal culture and specimens for confirmatory nucleic acid amplification testing and repeat *N. gonorrhoeae* serine 91 *gyrA* testing during the enrollment visit. We determined the ciprofloxacin minimum inhibitory concentration for gonococcal isolates by agar dilution performed at the University of Washington Neisseria Reference Laboratory. Subjects were treated with a single oral tablet of ciprofloxacin 500 mg and returned for a test of cure visit at 5–10 days. Ciprofloxacin administration was observed in the clinic.

Study Oversight

Each clinical site obtained institutional review board approval through a local or central institution. At the time of enrollment, trained study staff obtained written documentation of informed consent for each subject. The National Institutes of Health Office of Clinical Research Affairs reviewed and approved the study protocol.

Subjects

Eligible subjects were age 18 years or older, provided informed consent, had untreated urogenital or rectal *N. gonorrhoeae* infection, no contraindications to ciprofloxacin treatment, and were willing to abstain from sexual intercourse or use condoms during any sexual contact until the test of cure visit. Some participants also had a pharyngeal *N. gonorrhoeae* infection and that anatomic site was evaluated in our study but was not used in the inclusion criteria. Women of childbearing potential were not pregnant or breastfeeding, used an effective birth control method for 30 days before enrollment, and agreed to continue the use of birth control through study follow-up. All subjects also agreed to avoid magnesium/aluminum antacids, sucralfate, didanosine, or highly buffered drugs up to 2 hours after ingestion of study drug.

Individuals were excluded if they received any systemic or local antibiotic therapy in the 30 days prior to enrollment, had known renal insufficiency, used systemic corticosteroid drugs or other immunosuppressive therapy within 30 days prior to enrollment, or received or planned to receive an investigational product in a clinical trial within 30 days prior to or 7 days after ciprofloxacin treatment. We excluded those with a clinical diagnosis of epididymitis, pelvic inflammatory disease, or genital ulcer disease. A sample size of 257 was set as the target for the study to provide 80% power to detect a microbiological cure rate of at least 95%; however, the study met the targeted precision of the effect estimate sooner and therefore the study was completed with fewer subjects.

Efficacy Outcomes

The primary outcome was microbiological cure (ie, negative culture for *N. gonorrhoeae*) at 5–10 days after therapy. We analyzed the outcome among all subjects with culture-positive infections at enrollment as well as by the individual anatomic site of infection. Outcomes were reported both by subject and by individual infection in those with multiple infections.

Statistical Analysis

Efficacy analyses were performed in multiple analysis populations. The intent-to-treat population included all subjects enrolled who had a culture-positive *N. gonorrhoeae* infection at enrollment regardless of the enrollment repeat *gyrA* serine 91 *N. gonorrhoeae* result. The microbiological intent-to-treat population for the specified anatomic site included only those with a *gyrA* serine 91 wild-type *N. gonorrhoeae* culture-positive result at enrollment. Those who did not have evaluable culture results available at follow-up (eg, lost to follow-up, follow-up outside of prespecified study follow-up visit window, or culture not performed) were categorized as microbiological failures in the intent-to-treat and microbiological intent-to-treat populations. The per-protocol population, our primary outcome analysis population, for the specified anatomic site included those in the microbiological intent-to-treat population with a follow-up culture result collected within the protocol-specified window (ie, 5–10 days after enrollment) and who did not receive any contraindicated medication or systemic antibiotic prior to the follow-up visit.

We calculated the proportion cured as the proportion of infections with a negative culture at follow-up. One-sided 95% Jeffreys confidence intervals (CIs) were computed [19].

We compared the minimum inhibitory concentration results with the *gyrA* serine 91 *N. gonorrhoeae* genotyping results. We categorized an infection as ciprofloxacin susceptible if the minimum inhibitory concentration for the isolate was less than 1.0 μg/mL [20].

RESULTS

Two hundred thirty-two subjects were screened, resulting in 211 enrolled subjects. Of the enrolled subjects, there were 106 subjects with 117 *N. gonorrhoeae* culture-positive infections with wild-type *gyrA* serine 91 *N. gonorrhoeae* genotype included in the per-protocol analyses of microbiological cure at individual anatomic sites. Subjects were excluded from the per-protocol analyses due to a combination of exclusion criteria including the following: not having a baseline culture-positive *gyrA* serine 91 wild-type *N. gonorrhoeae* infection at any anatomic site (n = 95), not meeting the other inclusion criteria (n = 6), not completing the test of cure visit per protocol (n = 7 terminated the study prior to the test; n = 2 completed the visit outside the 5–10-day test of cure visit window), not having a determinate culture result at follow-up (n = 2), and receiving a contraindicated medication/systemic antibiotic prior to the test of cure assessment (n = 1).

Table 1. Characteristics of the Per-Protocol Study Population, Gyrase A Serine 91 *Neisseria gonorrhoeae* Ciprofloxacin Treatment Study

	n	%
Age, mean (SD), years	28.1 (7.9)	
Male	98	92.5
Sexual orientation		
Heterosexual/straight	16	15.1
Homosexual/gay/lesbian	73	68.9
Bisexual	14	13.2
Other/refused to answer	3	2.8
Geographic site		
AIDS Healthcare Foundation	4	3.8
Los Angeles LGBT Center	31	29.2
San Francisco Department of Public Health	16	15.1
Philadelphia Department of Public Health	33	31.1
University of Mississippi Medical Center	12	11.3
Louisiana State University	1	0.9
University of California San Diego Antiviral Research Center	1	0.9
Whitman-Walker Health	8	7.5
Race/cultural origin		
American Indian/Alaskan Native	2	1.9
Asian	7	6.6
Hawaiian/Pacific Islander	1	0.9
African American/black	29	27.4
White	57	53.8
Multiracial	5	4.7
Other/unknown	5	4.7
Hispanic ethnicity		
Non-Hispanic	76	71.7
Hispanic	30	28.3
Site of infection (n = 117 infections)		
Pharyngeal	14	12.0
Rectal	73	62.4
Cervical/urethral	30	25.6

N = 106.

Table 1 shows the distribution of subjects by study recruitment site, characteristics of study subjects, and anatomic sites of infection for the per-protocol population. Of the 117 infections, 73 were rectal, 30 were urethral/cervical, and 14 were pharyngeal.

Table 2 shows the treatment outcome results by study population. In the per-protocol population there was 100% microbiologic cure regardless of the anatomic site of infection in those with *gyrA* serine 91 wild-type *N. gonorrhoeae*. The 8 microbiological failures in the microbiological intent-to-treat population were all imputed (ie, statistically classified as failure) due to subjects terminating the study prior to the follow-up visit or not having culture results available at follow-up. In the full intent-to-treat population, there were 3 additional rectal microbiological failures, of which 2 subjects with non–wild-type *gyrA* serine 91 *N. gonorrhoeae* rectal infections detected at the enrollment visit and 1 subject had an indeterminate *gyrA* serine 91 *N. gonorrhoeae* result at enrollment, all culture positive at follow-up. Also, in the full intent-to-treat population there were 3 additional pharyngeal microbiological failures due to 1 subject with an indeterminate *gyrA* serine 91 *N. gonorrhoeae* result at the enrollment visit who was culture positive at follow-up (and that infection was characterized as non–wild-type *gyrA*) and 2 imputed failures due to early termination prior to the follow-up visit. Thus, the 4 observed cases of persistent culture positivity were infections at enrollment with either a non–wild-type *gyrA* serine 91 *N. gonorrhoeae* (n = 3) or indeterminate *gyrA* serine 91 *N. gonorrhoeae* (n = 1).

The wild-type *gyrA* serine 91 *N. gonorrhoeae* infections in the per-protocol population (N = 106) all had a ciprofloxacin minimum inhibitory concentration less than 1.0 μg/mL (susceptible). In those with urogenital infection, the median minimum inhibitory concentration was 0.004 μg/mL and the minimum inhibitory concentration 90% was 0.03 μg/mL or less. For those with rectal infections, the median minimum inhibitory concentration was 0.004 μg/mL and the minimum inhibitory concentration 90% equaled 0.008 μg/mL; and for pharyngeal infections, the median minimum inhibitory concentration was 0.004 μg/mL and minimum inhibitory concentration 90% equaled 0.008 μg/mL. Those results demonstrate 100% concordance between the *gyrA* serine 91 *N. gonorrhoeae* result and in vitro susceptibility.

Table 2. Microbiologic Cure by Anatomic Site and Study Population, Gyrase A Serine 91 *Neisseria gonorrhoeae* Ciprofloxacin Treatment Study

Study Population and Statistics	Cervical/Urethral	Rectal	Pharyngeal	All Anatomic Sites
Intent-to-treat[a]				
Number of infections with microbiological cure, n	38	81	35	154
Number of infections, n	39	89	40	168
Microbiological cure, %	97.4	91	87.5	91.7
95% CI, %	90.4–100.0	85.0–100.0	77.0–100.0	87.6–100.0
Microbiological intent-to-treat[b]				
Number of infections with microbiological cure, n	33	74	14	121
Number of infections, n	34	79	16	129
Microbiological cure, %	97.1	93.7	87.5	93.8
95% CI, %	89.1–100.0	88.0–100.0	69.5–100.0	89.6–100.0
Per-protocol[c]				
Number of infections with microbiological cure, n	30	73	14	117
Number of infections, n	30	73	14	117
Microbiological cure, %	100	100	100	100
95% CI, %	90.5–100.0	96.0–100.0	80.7–100.0	97.5–100.0

Abbreviation: CI, confidence interval.

[a]The intent-to-treat population included all infections in subjects enrolled who had a culture-positive *N. gonorrhoeae* infection at enrollment regardless of repeat *gyrA* serine 91 *N. gonorrhoeae* result at enrollment.

[b]The microbiological intent-to-treat population for the specified anatomic site included only those with a wild-type *gyrA* serine 91 *N. gonorrhoeae* culture-positive result at enrollment.

[c]The per-protocol population for the specified anatomic site included those in the microbiological intent-to-treat population with a follow-up culture result collected within the protocol-specified follow-up visit window (ie, 5–10 days after enrollment) and who did not receive any contraindicated medication or systemic antibiotic prior to the follow-up visit.

DISCUSSION

We conducted a prospective clinical study of single-dose oral ciprofloxacin treatment in subjects with culture-positive *gyrA* serine 91 wild-type *N. gonorrhoeae* infections. A laboratory-developed PCR assay determined *gyrA* serine 91 *N. gonorrhoeae* genotype status. We observed 100% cure in those subjects who were culture positive at enrollment with the wild-type *gyrA* serine 91 *N. gonorrhoeae* genotype.

Our results confirm a prior small retrospective study among patients with *gyrA* serine 91 wild-type *N. gonorrhoeae* infections who also had 100% cure as determined by follow-up gonococcal nucleic acid amplification testing [17]. Using a prospective study design, larger sample size, and microbiologic culture as the test of cure, the gold standard for the detection of *N. gonorrhoeae* infection, our results provide very strong evidence that the *gyrA* serine 91 *N. gonorrhoeae* genotype reliably predicts clinical outcome in patients treated with ciprofloxacin.

While the analyses of the intent-to-treat and microbiological intent-to-treat populations demonstrated less than 100% cure, none of the wild-type *gyrA* serine 91 *N. gonorrhoeae* treatment failures were true microbiological failures. Of the 2 subjects with culture-positive *N. gonorrhoeae* infections at enrollment with non–wild-type serine 91 *gyrA* genotype, both failed treatment with persistent culture-positive infection at follow-up, providing further support of the clinical implications of the serine 91 *gyrA* genotype. Our prior work and that of others has shown that non–wild-type *gyrA* serine 91 *N. gonorrhoeae* genotype infections are associated with elevated ciprofloxacin minimum inhibitory concentrations in vitro [15, 21].

The use of molecular microbial genotypic assays to predict antimicrobial susceptibility in bacteria and guide clinical practice is not new and has been applied in *Mycobacterium tuberculosis* infections [22], *Staphylococcus aureus* infections [23], and more recently, *Enterobacteriaceae* [24]. However, there are very few prospective studies using molecular methods to predict antimicrobial susceptibility along with clinical outcomes and none using these methods in the context of increasingly antimicrobial resistant *N. gonorrhoeae*.

The limitations of our study include the modest sample size, resulting in less-precise efficacy estimates by the anatomic site of infection. Due to the turnaround time for *gyrA* serine 91 *N. gonorrhoeae* testing in our study, participation was also limited to asymptomatic individuals with gonococcal infections detected in screening specimens. In the future, more rapid point-of-care tests that detect both *N. gonorrhoeae* and markers of resistance will enable the timely resistance-guided treatment of both asymptomatic and symptomatic patients. Furthermore, there were a few cases where the screening *gyrA* test indicated wild-type infection and the repeat test done at enrollment indicated non–wild-type or indeterminate *gyrA*; thus, while those infections are included in our intent-to-treat analytic populations, they were excluded from the per-protocol population. In those cases, there may have been a mixed infection.

Our findings support the use of *gyrA* serine 91 genotyping to predict the ciprofloxacin susceptibility of *N. gonorrhoeae* to guide antimicrobial therapy. Recognizing the potential of such genotyping systems to enhance the treatment of gonorrhea and contribute to the potential slowing of the emergence of antimicrobial resistance in *N. gonorrhoeae*, the British Association for Sexual

Health and HIV updated its gonorrhea treatment guidelines to recommend the use of ciprofloxacin treatment when ciprofloxacin susceptibility is known [25]. Prior work has shown the ease of integration of *gyrA* serine 91 *N. gonorrhoeae* genotyping into a large health system, the acceptability of molecular test results among treating clinicians, and the impact on clinical treatment practices with a resultant reduction in the use of ceftriaxone [26].

The benefits of using ciprofloxacin to treat gonorrhea in the United States may be substantial. Antimicrobial-resistance surveillance data from the CDC suggest that approximately 70% of *N. gonorrhoeae* infections may be susceptible to ciprofloxacin, with even higher proportions in certain subpopulations (eg, women, heterosexuals, and African-Americans) [27]. The use of *gyrA* serine 91 *N. gonorrhoeae* assay-guided ciprofloxacin therapy could lower the overall cost of treatment [28], reduce the need for repeat clinical visits for intramuscular therapy and provide a simple alternative treatment option for those with an allergy to B-lactam ring-containing antibiotics. Last, the use of single-dose oral ciprofloxacin, a safe, well-tolerated, and inexpensive antibiotic, would facilitate the treatment of sex partners through expedited-partner therapy—an evidence-based practice to reduce gonococcal reinfection [29].

In conclusion, we found that a molecular assay to detect the wild-type serine 91 genotype of the *gyrA* gene of *N. gonorrhoeae* was highly predictive of a successful treatment outcome in subjects with gonococcal infections treated with ciprofloxacin. The widespread introduction and scale-up of *gyrA* serine 91 genotyping in *N. gonorrhoeae* infections could have substantial medical and public health benefits in settings where the majority of gonococcal infections are ciprofloxacin susceptible.

Notes

Acknowledgments. The authors acknowledge the scientific and programmatic guidance of Peter Wolff, MPA, and Carolyn Deal, PhD, of the Division of Microbiology and Infectious Diseases, US National Institutes of Health. They thank the subjects and clinic staff for their participation and support in this study. The authors acknowledge the original contributions of Mark Pandori, PhD, and Mark Siedner, MD, MPH, in the development of the *Neisseria gonorrhoeae* gyrase A serine 91 assay in 2005 and 2006.

Disclaimer. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the US National Institutes of Health.

Financial support. The National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), and the Division of Microbiology and Infectious Diseases provided financial support for the STAR Sexually Transmitted Infections Clinical Trials Group (STAR STI CTG) and protocol sites (contract HHSN272201300014I/HSN27200006). C. C. B. acknowledges funding from NIAID (award number K01AI136725). O. O. S. acknowledges funding from Social & Scientific Systems Inc.

Potential conflicts of interest. J. D. K. reports advisory board fees and nonfinancial support from Cepheid; consulting fees from BioFire, Shield Bio, and SpeedX; and research study support from Hologic, Gilead, Abbvie, SpeedX, and Visby Medical, outside the submitted work. S. N. T. reports grants from GlaxoSmithKline and AstraZeneca/Entasis, outside the submitted work. C. C. B. reports speaker's bureau fees from Cepheid Inc, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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