The Journal of Infectious Diseases

CORRESPONDENCE

Six *penA* Codons Accurately and Reliably Predict Cefixime-Decreased Susceptibility in *Neisseria gonorrhoeae*

To the Editor—We read with great interest the article by Thomas et al [1], describing the whole-genome-sequencing data of 649 US-based *Neisseria gonorrhoeae* strains with decreased susceptibility to cephalosporins and azithromycin collected through the Centers for Disease Control's Gonococcal Isolate Surveillance Project. The World Health Organization recommends cefixime, an oral third-generation cephalosporin, for the treatment of gonorrhea either in combination with 1 gram of oral azithromycin or alone as a single drug if recent local resistance data confirm susceptibility [2]. Previous investigators have shown that infections with gonococcal strains with a cefixime minimum inhibitory concentration (MIC) ≥0.12 μg/mL were significantly more likely to fail cefixime treatment than strains with MIC <0.12 μg/mL. Among the 649 strains, 121 had cefixime-decreased susceptibility (defined as MIC ≥0.12 μg/mL) [3].

We previously described that the *penA* gene for *N gonorrhoeae* penicillin-binding protein-2 reliably predicts cefixime-decreased susceptibility [4]. We found 6 codons in *penA* (amino acid position 375–377, 501, 542, and 551) that, when any 1 codon was mutated, predicted cefixime-decreased susceptibility in 413 (99.5%) of those 415 strains collected globally between 1996 and 2017 [4].

Using sequence data from the additional 121 strains with decreased susceptibility to cefixime reported by Thomas et al [1], our 6-codon algorithm correctly predicted cefixime-decreased susceptibility in 115 (95.9%). Combining our prior work with that of Thomas et al [1], the accuracy was 528 (98.5%) of 536. The genetic and epidemiologic characteristics of the 8 strains that were not identified by our algorithm are varied and do not contain the typical mosaic *penA* mutations associated with extended-spectrum cephalosporin-decreased susceptibility (Table 1).

We have verified that the parsimonious 6-codon molecular assay that we recently proposed would successfully predict cefixime-decreased susceptibility in a very high proportion of *N gonorrhoeae* strains with cefixime-decreased susceptibility currently circulating. We propose that surveillance efforts monitor mutations in those 6 codons in *penA* using real-time polymerase chain reaction methods [5] to supplement conventional phenotypic monitoring of antimicrobial resistance in *N gonorrhoeae*.

In addition, the development and implementation of such an assay for clinical use could make cefixime an effective alternative to dual therapy or injectable high-dose ceftriaxone therapy in settings where cefixime-decreased susceptibility is a concern [6]. In settings where cefixime-decreased susceptibility is rare, resistance-guided therapy could help slow down the continued emergence of antimicrobial resistance in *N gonorrhoeae.*

Notes

Financial support. Funding was provided by the National Institute of Allergy and Infectious Diseases, Grant R21 AI117256 (to J. D. K.).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Xiaomeng Deng[1] and Jeffrey D. Klausner[1,2,3]

[1]David Geffen School of Medicine, University of California Los Angeles, California, USA, [2]Division of Infectious Disease, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, California, USA, [3]Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, California, USA

References

1. Thomas JC, Seby S, Abrams AJ, et al. Evidence of recent genomic evolution

Table 1. Characteristics of the 8 Cefixime-Decreased Susceptible Gonococcal Strains That Had No Alterations at Amino Acid Position 375–377, 501, 542, or 551 of *penA*

Reference	Accession Number	Year of Collection	Country of Collection	*penA* type by NG-STAR[a]	Cefixime MIC (μg/mL)
[7]	No report	2013	Spain	Resembling 36[b]	≥0.125[c]
	No report	2013	Spain	Resembling 36[b]	≥0.125[c]
[1]	SRR8071198	2014	USA	2	0.125
	SRR8071266	2015	USA	14	0.125
	SRR8071414	2016	USA	14	0.125
	SRR8071120	2014	USA	19	0.125
	SRR8071395	2016	USA	19	0.125
	SRR5990438	2016	USA	68	0.25

Abbreviations: MIC, minimum inhibitory concentration; NG-STAR, *Neisseria gonorrhoeae* sequence typing for antimicrobial resistance.

[a]*Neisseria gonorrhoeae* sequence typing for antimicrobial resistance (https://ngstar.canada.ca).

[b]Complete nucleotide or amino acid sequence data were not reported by the authors.

[c]Specific MIC value was not reported by the authors.

Downloaded from https://academic.oup.com/jid/article/221/5/851/5580744 by Univ of Southern California user on 05 January 2022

in gonococcal strains with decreased susceptibility to cephalosporins or azithromycin in the United States, 2014-2016. J Infect Dis **2019**; 220:294–305.
2. World Health Organization. WHO guidelines for the treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization, **2016**.
3. Allen VG, Mitterni L, Seah C, et al. Neisseria gonorrhoeae treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA **2013**; 309:163–170.
4. Deng X, Allan-Blitz LT, Klausner JD. Using the genetic characteristics of *Neisseria gonorrhoeae* strains with decreased susceptibility to cefixime to develop a molecular assay to predict cefixime susceptibility. Sex Health **2019**; 16:488–499.
5. Wong L, Hemarajata P, Soge O, Humphries R, Klausner J. Real-time PCR targeting the penA mosaic XXXIV type for prediction of extended-spectrum-cephalosporin susceptibility in clinical *Neisseria gonorrhoeae* isolates. Antimicrob Agents Chemother **2017**; 61.
6. Wi T, Lahra MM, Ndowa F, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action. PLoS Med **2017**; 14:e1002344.
7. Serra-Pladevall J, Barberá MJ, Rodriguez S, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility in Barcelona: penA, ponA, mtrR, and porB mutations and NG-MAST sequence types associated with decreased susceptibility to cephalosporins. Eur J Clin Microbiol Infect Dis **2016**; 35:1549–56.

Received 15 August 2019; editorial decision 24 September 2019; accepted 2 October 2019; published online October 3, 2019.

Correspondence: J. D. Klausner, MD, MPH, 10920 Wilshire Blvd, Suite 350, Los Angeles, CA 90024 (jdklausner@mednet.ucla.edu).

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
DOI: 10.1093/infdis/jiz504

Reply: Evidence of Recent Genomic Evolution in Gonococcal Strains With Decreased Susceptibility to Cephalosporins or Azithromycin in the United States, 2014–2016

To the Editor—We would like to extend our gratitude to Drs. Deng and Klausner for their interest in our article, in which we phylogenetically characterized gonococcal isolates collected through national sentinel surveillance and circulating in the United States, between 2014 and 2016 [1]. We identified 2 major subpopulations of strains associated with reduced susceptibility to either azithromycin (multilocus sequence typing [MLST] ST9363) or cephalosporins (MLST ST1901), and we detailed the evolution of several strains that possessed mutations that were not observed in the United States in 2000–2013.

Antimicrobial resistance (AMR) in the gonococcus represents a major public health threat, chiefly due to its rapidly evolving nature and the increasingly limited number of available treatment options. Although routine surveillance of AMR in circulating strains is essential in monitoring this threat, an equally important practice involves the promotion of antibiotic stewardship in limiting the spread of resistance. It is notable that the Centers for Disease Control and Prevention's Gonococcal Isolate Surveillance Project, a historic sentinel surveillance program, has tracked AMR trends for over 30 years and, more recently, included whole-genome sequencing (WGS) of a subset of isolates [2]. As a result, the implementation of WGS has generated massive quantities of genomic data that can be used in tandem with data from traditional antimicrobial susceptibility testing to examine AMR trends. In addition, the release of these data to the public repositories has facilitated the ability of other investigators to conduct a myriad of follow-up studies.

We read with great interest the article by Deng et al [3], a follow-up to their recently published review of 415 international isolates with reduced cefixime susceptibility, describing a 6-codon algorithm that accurately predicts decreased cefixime susceptibility from *penA* alleles, and we believe it may provide a promising next step in the development of molecular assays for use in clinical settings. Diagnostic point-of-care tests could represent a potential paradigm shift in patient diagnosis and treatment, by providing clinicians with the simultaneous ability to rapidly screen gonococcal infections of concern and provide personalized patient care. Although unlikely to return to generally recommended usage, historically recommended drugs for empiric treatment (eg, ciprofloxacin, cefixime) could be effective treatments in patients identified with susceptible gonococcal infections. Work such as described by Deng et [3] al greatly contributes to the exploration of this approach.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of Veterans Affairs or the National Institutes of Health.

Financial support. This work was funded by the Centers for Disease Control and Prevention (CDC) and in part made possible through support from the CDC's Advanced Molecular Detection and Combating Antibiotic Resistant Bacteria programs. This project was also supported in part by an appointment to the Research Participation Program at the CDC administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the CDC. W. M. S. was supported by National Institutes of Health Grant R37AI21150-33 and funds from an Intergovernmental Personnel Act from the CDC and a Senior Research Career Scientist Award from the Biomedical Laboratory Research and Development Service of the US Department of Veterans Affairs.

Potential conflicts of interest. All authors: No reported conflicts. All authors

Downloaded from https://academic.oup.com/jid/article/221/5/851/5580744 by Univ of Southern California user on 05 January 2022