Cephalosporin Resistance in *Neisseria gonorrhoeae* Infections

To the Editor: The emergence of extended-spectrum cephalosporin resistance in *Neisseria gonorrhoeae* infections in North America and worldwide is worrisome, as is the current US response to that problem.[1] Authorities call for adherence to treatment recommendations, use of test of cure, risk-reduction counseling, increased condom use, clinician vigilance for treatment failure, and novel antimicrobial development.[2] Even though these measures are reasonable, none has been shown to reduce the population-level ecological effects of drug-resistant organisms.

However, the reduction in use of the antibiotic of concern is an intervention that has been successful. In the early 1990s, there was a major increase in erythromycin resistance among group A streptococci in Finland.[3] In response, national policies were instituted to reduce the use of macrolide antibiotics in outpatients. Between 1991 and 1992, there was a marked 50% reduction in erythromycin use, followed by a subsequent large decrease in the prevalence of erythromycin-resistant group A streptococcal infections (16.5% to 8.6%).

Even though symptomatic cases often are treated empirically at the time of their clinic visit, overall just under half of patients (46.1% [1380/2996]) seen in 12 Los Angeles County Department of Public Health and 2 community sexually transmitted disease clinics in 2011 were treated within 3 to 30 days after their test results became available. The treatment of gonorrhea could be substantially modified by the use of real-time antimicrobial susceptibility testing. For example, the addition of a molecular marker of ciprofloxacin susceptibility could be incorporated into existing nucleic acid amplification tests for *N gonorrhoeae* detection,[4] similar to current molecular-based tests for *Mycobacterium tuberculosis* detection and rifampin susceptibility.[5] Such real-time susceptibility testing would allow the clinician the opportunity to make an informed antibiotic treatment choice.

Currently about 85% to 90% of *N gonorrhoeae* cases are susceptible to ciprofloxacin. Modifications to existing tests are not inexpensive and will require the encouragement of state and federal policy makers to ensure additional test development. Such a strategy could result in a delay in the emergence of resistance to the last class of antibiotic treatment for gonorrhea and perhaps even result in an increase in drug susceptibility to a previously effective treatment regimen. Resources must be used wisely and evidence-based interventions must be developed to stem the tide of extremely drug-resistant gonorrhea.

Jeffrey D. Klausner, MD, MPH
Peter Kerndt, MD, MPH

Author Affiliations: Department of Medicine, UCLA David Geffen School of Medicine, Los Angeles, California (Dr Klausner; jdklausner@mednet.ucla.edu); and Los Angeles County Department of Public Health, Los Angeles, California (Dr Kerndt).
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1. Allen VG, Mitterni L, Seah C, et al. *Neisseria gonorrhoeae* treatment failure and susceptibility to cefixime in Toronto, Canada. *JAMA*. 2013;309(2):163-170.
2. Kirkcaldy RD, Bolan GA, Wasserheit JN. Cephalosporin-resistant gonorrhea in North America. *JAMA*. 2013;309(2):185-187.
3. Seppälä H, Klaukka T, Vuopio-Varkila J, et al; Finnish Study Group for Antimicrobial Resistance. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med*. 1997;337(7):441-446.
4. Siedner MJ, Pandori M, Castro L, et al. Real-time PCR assay for detection of quinolone-resistant *Neisseria gonorrhoeae* in urine samples. *J Clin Microbiol*. 2007;45(4):1250-1254.
5. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005-1015.

In Reply: Drs Klausner and Kerndt highlight the urgent need for innovative approaches to address the continued emergence of multidrug-resistant *N gonorrhoeae*. Specifically, by analogy to efforts successful at reducing macrolide-resistant group A streptococci, they suggest real-time detection and antimicrobial testing use may turn the tide of cephalosporin resistance in *N gonorrhoeae*.

Point-of-care diagnostics that enable the detection of gonorrhea and markers of antibiotic resistance are feasible and offer great promise in facilitating public health control of gonorrhea, including slowing the development of cephalosporin resistance. However, evidence that the introduction of these tests would reverse preexisting levels of cephalosporin resistance in *N gonorrhoeae* is less certain. Once established, preexisting rates of resistance to antibiotics tend to persist in *N gonorrhoeae*.

For example, data from the Gonococcal Isolate Surveillance Network reveal that 13.3% of isolates were resistant to ciprofloxacin in 2011 despite removing ciprofloxacin as

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the recommended therapy in 2007, the time when ciprofloxacin resistance peaked at 14.8%.[1] The main reasons hypothesized to explain the persistence of antimicrobial resistance in this organism are (1) ongoing selective pressure due to use for other indications and (2) the lack of overall fitness cost to the organism associated with resistance.[2]

Evidence of the ongoing fitness of resistant strains of *N gonorrhoeae* was demonstrated by studies in a competitive murine model; isolates of *N gonorrhoeae* with first-step mutations of ciprofloxacin resistance in *gyrA* demonstrated increased fitness compared with parent strains without this mutation.[3] Furthermore, even though the addition of a second-step mutation in *parC* leads to decreased fitness in vivo, a compensatory mutation was detected in a subset of these isolates and was associated with restored fitness compared with the susceptible parent strain.

Equally important to the control of antimicrobial resistance is the optimization of pharmacokinetic and pharmacodynamic parameters of recommended antimicrobials for the treatment of gonorrhea, which is another intervention that has demonstrated the ability to slow the rate of antimicrobial resistance at a population level. In one study,[4] investigators described the increased use of ciprofloxacin for respiratory infections in Canada that was associated with a rapid increase in ciprofloxacin-resistant *Streptococcus pneumonia*e in the 1990s.

With a switch to more potent respiratory fluoroquinolones, the rates of fluoroquinolone resistance in circulating strains of *S pneumoniae* stabilized despite the doubling of fluoroquinolone use to treat respiratory infections from 1998 through 2009. New approaches to antibiotic-resistant *N gonorrhoeae* are important to ensure the ongoing success of public health interventions. Increased and multiple doses of current classes of antimicrobials may offer only short-term solutions. Concurrent strategies are needed to avoid selection and maintenance of resistance to antimicrobial therapies for *N gonorrhoeae*.

Other options may include the use of effective combination therapies, strategies to diagnose and eradicate asymptomatic reservoirs for resistant *N gonorrhoeae*, such as the pharynx,[5] and the increased feasibility of a *N gonorrhoeae* vaccine, given genomic advances that have led to the recent development of the analogous serogroup B meningococcal vaccine.[6]

Vanessa G. Allen, MD, MPH
Roberto G. Melano, PhD
Donald E. Low, MD

Author Affiliations: Public Health Ontario, Toronto, Canada (Drs Allen and Melano) (vanessa.allen@oahpp.ca); and Mt Sinai Hospital, Toronto, Ontario, Canada (Dr Low).

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1. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2011. http://www.cdc.gov/std/stats11/default.htm. Accessed February 18, 2013.
2. Unemo M, Shafer WM. Antibiotic resistance in *Neisseria gonorrhoeae:* origin, evolution, and lessons learned for the future. *Ann N Y Acad Sci*. 2011;1230:E19-E28.
3. Kunz AN, Begum AA, Wu H, et al. Impact of fluoroquinolone resistance mutations on gonococcal fitness and in vivo selection for compensatory mutations. *J Infect Dis*. 2012;205(12):1821-1829.
4. Patel SN, McGeer A, Melano R, et al; Canadian Bacterial Surveillance Network. Susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *Antimicrob Agents Chemother*. 2011;55(8):3703-3708.
5. Barbee LA, Kerani RP, Dombrowski JC, Soge OO, Golden MR. A retrospective comparative study of 2-drug oral and intramuscular cephalosporin treatment regimens for pharyngeal gonorrhea [published online March 13, 2013]. *Clin Infect Dis*. doi:10.1093/cid/cit084.
6. Gossger N, Snape MD, Yu LM, et al; European MenB Vaccine Study Group. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA*. 2012;307(6):573-582.

In Reply: We agree with Drs Klausner and Kerndt that antibiotic stewardship is an important component of controlling antibiotic resistance, and we support such efforts as sound clinical and public health practice. For many bacterial pathogens, antibiotic consumption appears to promote the emergence of resistance, and judicious antibiotic use may reduce the prevalence of resistance.[1]

However, for several reasons, it is not at all clear that improved antibiotic stewardship in the United States would prevent the emergence of cephalosporin resistance in *N gonorrhoeae*. First, gonococcal resistance is a global phenomenon, and importation of resistant strains from other countries appears to play a large role in the emergence of resistance in the United States. Gonococcal resistance phenotypes tend to emerge initially in East Asia before spreading globally.[2] When resistance has emerged in the United States, it has appeared first in geographic regions in relative proximity to Asia such as Hawaii and the West Coast.

Second, resistance has emerged first in the western United States, yet the West has the lowest per capita antimicrobial prescription sales of all regions.[3] In addition, unlike some other bacterial pathogens, *N gonorrhoeae* maintains genetic resistance determinants even after the apparent removal of antibiotic selection pressure; some resistance determinants may actually provide a fitness advantage, even in the absence of antibiotics.[4,5]

The decline or discontinuation in the use of penicillin or fluoroquinolones for treatment of gonorrhea has not appreciably changed the prevalence of *N gonorrhoeae* resistance to these antibiotics in the United States.[6] It is possible that for selected antibiotics, such as macrolides, local antibiotic usage might influence resistance patterns and that domestic selection pressure due to antibiotic use for other indications might contribute to gonococcal resistance to some degree. This has not been clearly demonstrated. More research on the relationship between domestic antibiotic prescribing and the emergence or persistence of gonococcal resistance may prove helpful.

We agree with Klausner and Kerndt that real-time antimicrobial susceptibility testing or the addition of molecular markers of genetic resistance determinants to existing nucleic acid amplification tests could have the potential to

guide the choice of antibiotics, so that ideally the most effective antibiotic can be prescribed at the time of diagnosis. At this time, however, antimicrobial susceptibility testing for *N gonorrhoeae* is not widely available. It requires culture of the live organism, and culture is done infrequently in most clinical settings and laboratories.

Incorporating assays for well-characterized resistance genotypes, such as for ciprofloxacin resistance, into nucleic acid amplification tests does hold promise. Research to develop both nonculture tests for gonococcal antimicrobial susceptibility and new antimicrobial agents will be a key component of an effective response to the threat of antimicrobial-resistant *N gonorrhoeae*.

Robert D. Kirkcaldy, MD, MPH
Gail A. Bolan, MD
Judith N. Wasserheit, MD, MPH

Author Affiliations: Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia (Drs Kirkcaldy and Bolan) (rkirkcaldy@cdc.gov); and Department of Global Health, University of Washington, Seattle (Dr Wasserheit).
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1. Willmann M, Marschal M, Hölzl F, et al. Time series analysis as a tool to predict the impact of antimicrobial restriction in antibiotic stewardship programs using the example of multidrug-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2013;57(4):1797-1803.
2. Ross JDC. Fluoroquinolone resistance in gonorrhoea: how, where and so what. *Int J STD AIDS*. 1998;9(6):318-322.
3. Hicks LA, Suda KJ, Robert RM, Hunkler R, Taylor TH, Danziger LH. Antimicrobial prescription data reveal wide geographic variability in antimicrobial use in the United States, 2009. Presented at: 48th Annual Meeting of the Infectious Disease Society of America; October 21-24, 2010; Vancouver, British Columbia, Canada. Abstract 339.
4. Unemo M, Shafer WM. Antibiotic resistance in *Neisseria gonorrhoeae*: origin, evolution, and lessons learned for the future. *Ann N Y Acad Sci*. 2011;1230:E19-E28.
5. Kunz AN, Begum AA, Wu H, et al. Impact of fluoroquinolone resistance mutations on gonococcal fitness and in vivo selection for compensatory mutations. *J Infect Dis*. 2012;205(12):1821-1829.
6. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2011. http://www.cdc.gov/std/stats11/default.htm. Accessed February 15, 2013.

Use of Administrative Data for Public Reporting of Outcomes

To the Editor: In their Viewpoint regarding the use of administrative data (ie, *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]*) in public reporting of outcomes and pay for performance, Dr Farmer and colleagues[1] argued for "a national, standardized system for outcome reporting" separate from administrative data that is "minimally affected by the incentives to alter coding created by public reporting." Count us as skeptics.

We contend that the key determinants of whether hospitals game the measurement of quality indicators are the ease of doing so and associated incentives and disincentives, not the type of data collected. Biased reporting is no more inherent to *ICD-9-CM* data, which were not developed for reimbursement, than it is to other types of clinical data. Voluntary registries, such as the National Surgical Quality Improvement Program, appear comparatively accurate, but they are not publicly available to hold hospitals accountable and they have limited participation, possibly enriched with hospitals providing higher quality care.[2]

The authors cited the National Healthcare Safety Network as an example of an effective reporting system. However, since the Centers for Medicare & Medicaid Services effectively mandated National Healthcare Safety Network-based reporting of central line–associated bloodstream infections (CLABSIs) in 2011, the incidence of reported CLABSIs decreased by 41% compared with decreases of 7% to 17% for other health care–associated infections, consistent with differential reporting.[3]

When data are collected to hold organizations accountable for their prices and outcomes, as stakeholders now demand[4] (and as needed to drive participation by reluctant organizations), hospitals become incentivized to have their outcomes look more favorable—and the gaming begins. The only means we foresee to avoid this problem are both mandated participation and verification through rigorous, frequent auditing, which may be both costly and politically untenable, especially for registries.

Ironically, administrative data may be best poised to serve this role because an auditing mechanism and legal disincentives to fraudulent coding already exist, even if they are less robust than they could be. Farmer et al[1] cited decreased rates of 2 patient safety indicators with the cessation of additional reimbursement in 2008. However, this payment rule virtually coincided with the requirement to use present-on-admission coding, which increased the accuracy of those indicators by minimizing the number of false-positive records. Accounting for this change, the reported decreases between 2008 and 2010 in *ICD-9-CM*-coded CLABSIs and retained foreign objects were only 15% and 23%, respectively, not 50%.[5]

Garth H. Utter, MD, MSc
Patrick S. Romano, MD, MPH

Author Affiliations: Departments of Surgery (Dr Utter; garth.utter@ucdmc.ucdavis.edu) and Internal Medicine (Dr Romano), University of California, Davis, Medical Center, Sacramento.
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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect those of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

1. Farmer SA, Black B, Bonow RO. Tension between quality measurement, public quality reporting, and pay for performance. *JAMA*. 2013;309(4):349-350.
2. Xian Y, Pan W, Peterson ED, et al; GWTG Steering Committee and Hospitals. Are quality improvements associated with the Get With the Guidelines-Coronary Artery Disease (GWTG-CAD) program sustained over time? a longitudinal comparison of GWTG-CAD hospitals versus non-GWTG-CAD hospitals. *Am Heart J*. 2010;159(2):207-214.
3. Centers for Disease Control and Prevention. National and state healthcare–associated infections standardized infection ratio report. http://www.cdc.gov/hai/pdfs/SIR/SIR-Report_02_07_2013.pdf. Accessed February 19, 2013.