

Emerging Trends in Antibiotic Resistant *Neisseria gonorrhoeae*: A National and Hawai'i Perspective

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Abstract

Gonorrhea is the second most common nationally notifiable infectious disease in the United States. Rates have been increasing nationally as have antibiotic-resistant isolates. Both the Centers for Disease Control and Prevention and the World Health Organization have recognized antibiotic-resistant Neisseria gonorrhoeae as a major public health threat and have warned of the emerging threat of "untreatable" gonorrhea. Hawai'i has been on the front lines nationally for gonococcal antimicrobial susceptibility surveillance due to its long-standing, statewide gonococcal isolate surveillance program coupled with antibiotic susceptibility testing of all isolates, and Hawai'i's geographic location between Asia where drug-resistant strains originate, and the continental United States. This article highlights emerging trends in and current status of antibiotic resistant Neisseria gonorrhoeae from a national and Hawai'i perspective.

Keywords

drug resistance, microbial; *Neisseria gonorrhoeae*

Abbreviations

AST = antibiotic susceptibility testing
CDC = Centers for Disease Control and Prevention
GISP = Gonococcal Isolate Surveillance Project
HDOH = Hawai'i Department of Health
NAAT = nucleic acid amplification test
STD = sexually transmitted disease
SURRG = Strengthening the US Response to Resistant Gonorrhea
WHO = World Health Organization

Introduction

Among reportable nationally notifiable infectious diseases in the United States (US), gonorrhea ranks second (surpassed only by chlamydia) and rates of gonorrhea have increased 75.2% since a historic low in 2009.¹ In addition, the emergence and spread of antimicrobial-resistant *Neisseria gonorrhoeae* has been recognized as a major public health threat by both the Centers for Disease Control and Prevention (CDC)² and the World Health Organization (WHO).³ Hawai'i has been at the forefront in recognition and early identification of resistant *N. gonorrhoeae* strains because of its long-standing, culture-based screening activities and the fact that Hawai'i is located between the continental US and Asia where these strains originate.⁴

Hawai'i is a national sentinel site for monitoring *N. gonorrhoeae* antibiotic susceptibility and has participated in the CDC's

Gonococcal Isolate Surveillance Project (GISP) since 1987.^{5,6} At each of 25-30 GISP sites, gonococcal isolates are collected each month from the first 25 men with gonococcal urethritis. The isolates are then transported to a regional laboratory for antibiotic susceptibility testing (AST) using the agar dilution method. The Hawai'i Department of Health (HDOH) Sexually Transmitted Disease (STD) Clinic was one of the original GISP sites; Tripler Army Medical Center became a GISP site in 2001.⁷ The regional laboratory for Hawai'i is at the University of Washington, Seattle.

While the vast majority of gonorrhea cases nationally are diagnosed using nucleic acid amplification tests (NAATs), The HDOH State Laboratory has maintained a state-wide gonococcal isolate surveillance program since the early 1970s and has provided culture-based diagnostic support to community health centers, family planning providers, college health clinics, and correctional facilities in addition to the public STD clinic.⁸ Culture isolates are obtained from approximately 25% of all gonorrhea cases diagnosed in Hawai'i,⁹ and all culture isolates undergo AST using Etest (bioMérieux, Marcy-l'Etoile, France) at the HDOH State Laboratory. Hawai'i's proportion of diagnosed gonorrhea cases from which isolates are obtained and tested for antibiotic susceptibility is much higher than any other state and substantially higher than the approximately 1% of gonorrhea patients sampled nationally through GISP.¹⁰

Historical Trends in Emerging Antibiotic Resistance

Sulfonamide antibiotics introduced in the 1930s were the first curative therapy for gonorrhea. However, by the 1940s, sulfonamide-resistant gonococcal strains were common, and the newly discovered medication, penicillin, became the drug of choice for gonorrhea.¹¹ Tetracycline and spectinomycin were alternative therapies for individuals with penicillin allergies. However, spectinomycin is ineffective against oropharyngeal infections and has not been available in the US since 2006.¹² By the 1970s, high-level resistance to penicillin was identified, and widespread resistance to both tetracycline and penicillin occurred by the 1980s. Of note, Hawai'i was one of the first states to identify gonococcal isolates demonstrating high-level resistance to penicillin.¹³ In the 1980s, the CDC recommended extended spectrum cephalosporins as the primary treatment for gonorrhea and listed fluoroquinolones as an alternate therapy for individuals unable to take cephalosporins.¹⁴ In 1991, GISP

identified the first fluoroquinolone-resistant gonococcal strains in Honolulu, Hawai‘i.¹⁴ Fluoroquinolone resistance subsequently became widespread and the CDC updated their STD treatment guidelines in 2007 to no longer recommend fluoroquinolones to treat gonococcal infections.¹⁵

Since 2010, the CDC has recommended dual therapy for gonorrhea. The initial recommended dual therapy was an extended spectrum cephalosporin **plus** azithromycin (preferred) or doxycycline to both optimize treatment success and slow the emergence of resistance. The recommended ceftriaxone dose was also doubled from the earlier, 2006 recommendations.^{16,17}

The first three cases of multidrug-resistant gonorrhea with decreased susceptibility to cefixime (an oral third generation cephalosporin) were identified through GISP from Hawai‘i in 2001.¹⁸ Again, the subsequent widespread development of strains with decreased susceptibility to cefixime led the CDC to remove oral cephalosporins as a recommended treatment modality for gonorrhea in 2012. Of note, the largest increases of cefixime-resistant *N. gonorrhoeae* in the US were observed in Hawai‘i: from 0% in 2006 to 17% in 2009.¹⁹

Azithromycin monotherapy (2 g orally) had been listed as an alternative therapy for persons unable to take cephalosporins. However, due to emerging macrolide resistance and documented treatment failures, the 2015 CDC Treatment Guidelines no longer recommended azithromycin monotherapy as an option.¹² Of note, the first gonococcal isolate in the US with high-level azithromycin resistance was identified in Honolulu, Hawai‘i through HDOH’s culture-based surveillance program in 2011.²⁰

Current Status

Clinicians are currently left with a single, first-line treatment recommendation from the CDC for gonorrhea: 250 mg ceftriaxone administered intramuscularly **plus** 1 g oral azithromycin.¹² Dual therapy with ceftriaxone plus doxycycline is no longer listed by the CDC as a “recommended” or “alternative” regimen due to the high prevalence of tetracycline resistant strains. The use of doxycycline as a second antibiotic in the dual therapy regimen is only for patients with azithromycin allergies.¹²

Due to the alarming intersection of continued emerging resistance and dwindling treatment options, both the CDC and WHO have openly expressed concerns about a not-so-distant future with untreatable gonorrhea.^{21,22}

To date, there have been no treatment failures in the US with the dual treatment regimen recommended by the CDC. However, treatment failures have been documented from the United Kingdom and Australia.²³⁻²⁶ Intravenous ertapenem (a carbapenem class antibiotic) was ultimately administered as a last resort treatment for at least two cases.

The first gonococcal isolates in the US demonstrating both decreased susceptibility to ceftriaxone and high-level resistance to azithromycin were identified in Hawai‘i between April and May 2016 through the HDOH culture-based gonococcal surveillance program.⁹ These isolates were also resistant to penicillin, tetracycline, and fluoroquinolones, and whole genome sequencing revealed genetic relatedness.²⁷ All seven patients were successfully treated with the recommended dual therapeutic regimen, but the isolates’ antibiotic susceptibility profile is the most worrisome to date in the US.⁹

The HDOH’s Diamond Head STD Clinic was one of nine funded sites selected by the CDC for their Strengthening the US Response to Resistant Gonorrhea (SURRG) initiative in 2016. Three goals of this ambitious program are to enhance domestic gonorrhea surveillance and infrastructure; build capacity for rapid detection and response to antibiotic-resistant gonorrhea through increasing culturing and local antibiotic susceptibility testing; and enhance rapid field investigation to stop the spread of resistant infections.²⁸

The CDC also recommends several additional steps clinicians can take to mitigate the emergence and spread of antibiotic-resistant gonococcal strains. These include eliciting sexual histories from their patients and at least annually screening persons at increased risk for gonorrhea at all exposed anatomical sites (genital, oropharyngeal, and rectal). Explicitly targeted are sexually active men who have sex with men, females less than 25 years of age, and females 25 years of age and older who are at increased risk for gonorrhea. Patients should be counseled on consistent condom usage, and clinicians should follow CDC dual therapy treatment recommendations.¹¹ Partner notification is an imperative component of STD control programs. Any sexual partners within the past 60 days of persons diagnosed with gonorrhea should be referred for evaluation, testing, and presumptive dual treatment.¹² Optimally, testing would entail collecting cultures with simultaneous NAATs from all exposed sites.

In addition to the HDOH’s activities, Hawai‘i healthcare providers can assist in early identification of antibiotic-resistant *N. gonorrhoeae* by culturing patients with symptomatic urethritis and cervicitis, and obtaining cultures from any patient who tests positive for gonorrhea by NAAT prior to initiating treatment. Cultures should also be collected from any person who has been sexually exposed to gonorrhea, at all exposed anatomical sites (genital, oropharyngeal, and rectal), prior to administering treatment.

Appropriate culture media for *N. gonorrhoeae* is Modified Thayer Martin or Martin Lewis, and growth is optimized if cultures are placed in a 5% CO₂ atmosphere. This can be accomplished with a CO₂ tablet or a candle jar. Cultures should also be incubated at 35⁰-36.5⁰ C.²⁹

Persistent symptoms after receipt of the CDC's recommended dual treatment regimen are much more likely due to reinfection than treatment failure as there have been no treatment failures to date in the US; hence, it is imperative to always obtain an adequate sexual history from all patients, especially symptomatic patients. If there is any question of treatment failure, please contact the HDOH STD Clinic as soon as possible and obtain cultures to allow for antibiotic susceptibility testing.

The staff at Diamond Head STD Clinic can assist in culture collection and they welcome your referrals. Please direct any questions related to specimen collection or patient referral for culture and treatment to the STD clinic disease intervention specialists. The website for the Harm Reduction Services Branch, Hawai'i Department of Health which administers the Diamond Head STD Clinic can be accessed at URL: <https://health.hawaii.gov/harmreduction>, and the clinic's main phone line is 808-733-9281.

Conflict of Interest

None of the authors identify any conflict of interest.

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