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Cluster of *Neisseria gonorrhoeae* Isolates With High-level Azithromycin Resistance and Decreased Ceftriaxone Susceptibility, Hawaii, 2016

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Abstract

Background—The Centers for Disease Control and Prevention (CDC) currently recommends dual therapy with ceftriaxone and azithromycin for gonorrhea to ensure effective treatment and slow emergence of antimicrobial resistance. Since 2013, the prevalence of reduced azithromycin susceptibility increased in the United States; however, these strains were highly susceptible to cephalosporins. We identified a cluster of *Neisseria gonorrhoeae* isolates with high-level azithromycin resistance, several of which also demonstrated decreased ceftriaxone susceptibility.

Methods—Eight *N. gonorrhoeae* isolates collected from 7 patients on Oahu, Hawaii, seen 21 April 2016 through 10 May 2016 underwent routine Etest antimicrobial susceptibility testing by the Hawaii Department of Health. All demonstrated elevated azithromycin minimum inhibitory concentrations (MICs) >256 μg/mL and elevated ceftriaxone MICs (≥0.125 μg/mL). Isolates were sent to the University of Washington and CDC for confirmatory agar dilution testing; sequence data were sent to CDC for analysis. All patients were interviewed and treated, and when possible, partners were interviewed, tested, and treated.

Results—All isolates had azithromycin MICs >16 μg/mL and 5 had ceftriaxone MICs = 0.125 μg/mL by agar dilution. All isolates were β-lactamase positive and were resistant to penicillin,

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tetracycline, and ciprofloxacin. Genomic analysis revealed genetic relatedness. No patients reported recent travel or antibiotic use, and no male patients reported male sex partners. All patients were successfully treated.

Conclusions—This cluster of genetically related gonococcal isolates with decreased ceftriaxone susceptibility and high-level azithromycin resistance may bring the threat of treatment failure in the United States with the current recommended dual therapy one step closer.

Keywords

gonorrhea; antimicrobial drug resistance

The emergence and spread of antimicrobial resistance in *Neisseria gonorrhoeae* has been identified as a major public health threat by both the World Health Organization [1] and the Centers for Disease Control and Prevention (CDC) [2]. Resistance to penicillin, tetracycline, and fluoroquinolones has successively developed, limiting the use of these antibiotics [3]. Since 2010, dual therapy with a cephalosporin plus either azithromycin (preferred) or doxycycline has been recommended to ensure effective therapy and slow the emergence of antimicrobial-resistant *N. gonorrhoeae* [4]. Decreasing susceptibility to cefixime in the United States and gonorrhea treatment failures identified in other countries led the CDC to recommend against cefixime as a first-line treatment modality [5], and by 2015, CDC recommended only the combination of ceftriaxone plus azithromycin [6]. Concerns about the potential for macrolide resistance prompted CDC to discourage the use of azithromycin as second-line monotherapy for persons allergic to cephalosporins [6]. The first strain of *N. gonorrhoeae* (H041) with “ceftriaxone resistance” was identified in Japan in 2009 [7].

Hawaii is a sentinel site for the CDC’s Gonococcal Isolate Surveillance Project (GISP), a US-based sentinel surveillance system that has monitored gonococcal susceptibility since 1987 and is considered a “port of import” for antimicrobial-resistant strains entering the United States from Asia [8, 9]. Hawaii was one of the first US states identified with gonococcal isolates demonstrating high-level resistance to penicillin [10] and fluoroquinolones [11] and decreased susceptibility to cefixime [12]. From 2006 through 2011, Hawaii had the largest percentage of gonococcal isolates with cefixime minimum inhibitory concentrations (MICs) ≥0.25 μg/ mL among GISP sites [5]. Hawaii was also the first state to identify an isolate with high-level resistance to azithromycin [13]. In addition, the Hawaii Department of Health (HDOH) has maintained an active state-wide gonococcal isolate surveillance program since the early 1970s. From 2010 through 2014, isolates from 963 (24%) of 3997 gonorrhea cases diagnosed in Hawaii (HDOH unpublished data) were obtained and tested. All gonococcal isolates in Hawaii have had antibiotic susceptibility testing by the state laboratory since the early 1990s [9, 13]. The proportion of diagnosed gonorrhea cases from which isolates were obtained for antibiotic susceptibility testing is higher than for any other state and substantially higher than the approximately 4% of male gonorrhea patients sampled nationally in GISP [9].

Although GISP data from 2014 demonstrated a sharp increase in the percentage of isolates with reduced azithromycin susceptibility (MICs ≥2 μg/mL)—from 0.6% in 2013 to 2.5% in 2014—no GISP isolates showed reduced susceptibility to both azithromycin and ceftriaxone

[14]. We report on a cluster of *N. gonorrhoeae* isolates identified on Oahu, Hawaii, that demonstrates both high-level resistance to azithromycin and decreased susceptibility to ceftriaxone.

METHODS

Cluster Identification

The HDOH State Laboratories Division routinely conducts antimicrobial susceptibility testing on all gonococcal isolates using Etest (bioMérieux, Marcy-l'Etoile, France). From 21 April 2016 through 10 May 2016, 8 *N. gonorrhoeae* isolates obtained from 7 patients on Oahu and tested for antimicrobial susceptibility by Etest demonstrated elevated azithromycin MICs >256 μl/mL and elevated ceftriaxone MICs ≥0.125 μg/mL; all were β-lactamase positive. Four of the 8 isolates were urethral specimens submitted to GISP for antimicrobial susceptibility testing and surveillance. All 8 isolates were sent to the University of Washington (UW), Seattle Neisseria Reference Laboratory (a GISP regional laboratory), and CDC for confirmatory agar dilution testing and confirmatory azithromycin Etest. Two isolates obtained from the same patient were sent for analysis as the Etest results differed and a coinfection with 2 separate strains was entertained [15]. Agar dilution antimicrobial susceptibility test results were used to define resistance or decreased susceptibility [16, 17]. MIC interpretive criteria were in accordance with the Clinical and Laboratory Standards Institute when available [18]. GISP surveillance definition of reduced susceptibility was used to interpret MICs for azithromycin, cefixime, and ceftriaxone [14]. Hawaii State Laboratories conducted pulsed-field gel electrophoresis (PFGE) and whole genome sequencing (MiSeq, Illumina, San Diego, California) of all isolates, and CDC conducted phylogenetic analyses. Patients were interviewed, and when possible, partners were interviewed, tested, and treated.

RESULTS

Laboratory Analyses

Upon confirmatory testing at the UW and CDC laboratories, all 8 isolates had azithromycin agar dilution MICs >16 μg/mL and >256 μg/mL by Etest. These MIC values are the highest dilutions tested for each method and reflect high-level azithromycin resistance. Ceftriaxone agar dilution MICs were 0.125 μg/mL for 5 isolates (reflecting decreased ceftriaxone susceptibility), 0.06 μg/mL for 2 isolates, and 0.03 μg/mL for 1 isolate. All isolates were resistant to penicillin (MICs >64 μg/mL), tetracycline (MICs ≥2 μg/mL), and ciprofloxacin (MICs ≥8 μg/mL). Gentamicin MICs were 8 μg/mL for 5 isolates and 4 μg/mL for 3 isolates. Agar dilution MIC results from the UW and CDC laboratories were the same or within ±1 doubling dilution (Table 1). PFGE patterns of the isolates were indistinguishable after Nhe I and Xba I restriction digests, but some polymorphisms were seen with Spe I. Genomic sequencing data demonstrated a tight cluster, suggesting clonal expansion of a single clade [20].

Case Investigation

All 7 patients were symptomatic with dysuria, penile discharge, or vaginal discharge at the time of specimen collection. Five patients (4 males and 1 female) were seen at the HDOH sexually transmitted disease (STD) clinic; 2 (both males) were seen in private practice settings. Isolates were from culture specimens obtained from the urethra (5 male patients), cervix (1 female patient), and/or urine (2 male patients). The 2 male patients with urine isolates were seen in private sector settings and had urine collected to evaluate possible urinary tract infections, 1 of whom also had a culture-positive urethral specimen. The female patient also tested positive for *Chlamydia trachomatis* by cervical nucleic acid amplification test (NAAT). None of the patients reported recent travel or antibiotic use within the past 60 days, and none of the male patients reported male sex partners. All but 1 were initially treated with 250 mg ceftriaxone intramuscularly (IM) plus 1 g oral azithromycin. The remaining patient was initially treated with 2 g oral azithromycin plus doxycycline 100 mg orally twice daily for 14 days by his primary care physician and was retreated with 250 mg ceftriaxone IM plus 1 g oral azithromycin by HDOH clinicians once the susceptibility results were available. All 6 males reported resolution of their symptoms after treatment. The sole female reported decreased vaginal discharge after treatment, and her follow-up pelvic examination 4 weeks after treatment was unremarkable. Six of the 7 patients (5 males and 1 female) were retested at the HDOH STD clinic. All 6 had negative cultures and NAATs from reported anatomic exposure sites (Table 2).

Contact Tracing

Eight recent (within the previous 60 days) unique partners were reported by our 7 patients. Four were locatable. One of the 2 partners reported by our sole female patient (patient 3) had been diagnosed with gonorrhea by urine NAAT (no culture obtained) in a private practice setting. Post-treatment test results were negative for gonorrhea and chlamydia. On interview, he admitted to contact with a female sex worker in Honolulu. Patient 3's second partner was asymptomatic, treated empirically as a contact to gonorrhea and chlamydia [6], and tested negative for gonorrhea and chlamydia. Patient 5's single female partner tested negative for gonorrhea and chlamydia by urine NAAT at a community health center.

Two male patients (patients 2 and 7) identified the same female sex worker from a Honolulu massage parlor as a recent contact. She was asymptomatic, treated empirically as a gonorrhea contact [6], and tested negative for gonorrhea by both cervical and pharyngeal culture and NAAT. Patient 7 reported contact with an additional female sex worker from a second massage parlor who was not locatable despite HDOH disease intervention specialist (DIS) personnel visiting both massage parlors. Field testing was offered on site; 4 of 7 female employees agreed to urine NAAT testing for gonorrhea and chlamydia (all tests were negative). None agreed to pharyngeal NAAT testing.

None of the other patients reported partners in common. Patient 1 named an unlocatable female sex worker. Patient 4 claimed that his single female partner was a Japanese national who had since returned to Japan and tested negative for gonorrhea in Japan. Patient 6 reported a single partner during the preceding 60 days but refused to share locatable information (Table 2).

DISCUSSION

We identified a cluster of gonococcal isolates with high-level resistance to azithromycin; resistance to penicillin, tetracycline, and ciprofloxacin; and for 5 isolates, decreased susceptibility to ceftriaxone by agar dilution. The number of isolates that demonstrated decreased ceftriaxone susceptibility would be higher if defined by Etest results. Agar dilution is considered the reference "gold standard" for determining MIC values for antimicrobial susceptibility testing of antibiotics against *N. gonorrhoeae* [16, 17]. However, as agar dilution testing is labor intensive, technically demanding, and time consuming, it is generally performed only by reference laboratories. Etest is less complex, faster, and easier to perform [21–24]. The 2 methods have demonstrated agreement (within ±1 doubling dilution) of 89%–95% for ceftriaxone MICs against *N. gonorrhoeae* isolates [21–23]. Ceftriaxone Etest MICs have shown both higher [24] and slightly lower [21] values relative to ceftriaxone agar dilution MICs.

While the cluster initially appeared to be epidemiologically unrelated, PFGE and whole genome sequencing analysis revealed genetic relatedness, and the HDOH DIS staff identified some commonalities. Two of the male patients identified the same female sex worker as a recent contact. An additional male had contact with a female sex worker, and a male partner of the sole female patient also reported contact with a female sex worker.

Among urethral gonococcal isolates tested by GISP during 2005–2013, no clear trends in azithromycin MICs were observed [25]. However, the prevalence of reduced susceptibility to azithromycin increased sharply between 2013 and 2014 [14]. In addition, a recent report from England documented a cluster of *N. gonorrhoeae* isolates that were highly resistant to azithromycin [26]. Notably, GISP isolates collected in 2014 with reduced azithromycin susceptibility were highly susceptible to cephalosporins [14]. A review of 62 490 isolates collected through GISP from 2005 through 2015 revealed only 3 with both reduced susceptibility to azithromycin and reduced susceptibility to ceftriaxone, and all had MICs at the breakpoint of reduced susceptibility (azithromycin MICs = 2 μg/mL and ceftriaxone MICs = 0.125 μg/mL). No isolates with dual reduced susceptibility have been identified since 2011, and none have had both reduced susceptibility to ceftriaxone plus high-level azithromycin resistance (CDC unpublished data). In contrast, this Hawaii cluster is concerning because all 8 isolates demonstrate high-level azithromycin resistance and resistance to penicillin, tetracycline, and ciprofloxacin; 5 of 8 also demonstrate decreased susceptibility to ceftriaxone by agar dilution; and all isolates showed genetic relatedness. Development of higher ceftriaxone MICs and widespread transmission of such strains may severely complicate gonorrhea treatment.

Intensive surveillance in Japan has not shown further dissemination of the H041 strain [27]. While this strain demonstrated a high ceftriaxone MIC (2 μg/mL by agar dilution), the Etest azithromycin MIC was noted to be 0.5–1 μg/mL [7, 28]. Other strains have since been reported from Japan demonstrating "azithromycin resistance" defined as MICs >0.5 μg/mL (none of which showed high-level resistance [MICs > 16 μg/mL]), and all were susceptible to ceftriaxone [29]. A new ceftriaxone-resistant strain (FC428) was recently reported from Japan that demonstrated an Etest ceftriaxone MIC = 0.5 μg/mL. However, the strain was

susceptible to azithromycin (Etest MIC = 0.25 μg/mL) [30]. To our knowledge, no isolates have previously been reported with both high-level azithromycin resistance and decreased ceftriaxone susceptibility.

A recent report from the United Kingdom documented a gonorrhea treatment failure with the recommended regimen of ceftriaxone 500 mg and azithromycin 1 g [31]. The pharyngeal isolate exhibited a ceftriaxone MIC = 0.25 μg/mL and azithromycin MIC = 1 μg/mL. In comparison, our isolates demonstrate much greater resistance to azithromycin, and in 5 isolates, ceftriaxone MICs were only a single dilution lower than the ceftriaxone MIC from the UK isolate, suggesting that if the strains identified in Hawaii develop higher ceftriaxone MICs, they may be capable of causing treatment failure.

Because reinfections are currently more likely than actual treatment failures due to resistant infections in the United States, patients with possible treatment failure (persistent symptoms after appropriate therapy) should have specimens collected for culture and antimicrobial susceptibility testing and be retreated with the recommended regimen of ceftriaxone plus azithromycin [6]. It is imperative that a complete sexual history be taken from all patients. In situations where treatment failure due to resistance is highly suspected (eg, persistent symptoms 3–5 days after receiving recommended treatment or positive NAAT ≥7 days after receiving recommended treatment when no sexual contact is reported), clinicians should notify their local STD program, specimens should be collected for cultures and antimicrobial susceptibility testing, and patients can be treated with the combination of gentamicin 240 mg IM plus azithromycin 2 g orally or gemifloxacin 320 mg plus azithromycin 2 g orally (although current gemifloxacin shortages limit the usefulness of this agent, and the efficacy of gemifloxacin might not be optimal in the setting of ciprofloxacin resistance) [6, 32]. The 2-g dose of azithromycin is associated with a high prevalence of gastrointestinal symptoms [32]. Gentamicin has potential oto- and nephrotoxicity, although this risk is thought to be low in otherwise healthy patients receiving single dose treatment [32]. However, the use of gentamicin plus azithromycin or gemifloxacin plus azithromycin may not be effective in the setting of high-level azithromycin resistance and ciprofloxacin resistance, as was seen in the current cluster, particularly when treating pharyngeal gonorrhea.

The threat of multidrug-resistant gonorrhea leading to treatment failure in the United States with the current recommended dual therapy remains present. Our findings underscore the value of CDC recommendations for laboratories to maintain or reestablish culture-based methods to detect antimicrobial-resistant *N. gonorrhoeae*, particularly for patients with possible treatment failure [33]. Obtaining cultures before treatment from persons either presumptively treated or found to be positive for gonorrhea by NAAT testing can be invaluable for rapid detection of resistance [13]. It is important that clinicians be on high alert so that treatment failures can be identified and reported promptly to the local department of health and CDC. Rapid detection and effective treatment may prevent sequelae, allow partners to be identified and treated in a timely manner, and prevent or slow further transmission of resistant strains.

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Table 1.

Cluster of *Neisseria gonorrhoeae* Isolates With High-level Azithromycin Resistance and Decreased Susceptibility to Ceftriaxone, Hawaii, April 2016–May 2016

Patient Number	Culture Site	β-Lactamase	Azithromycin MIC (μg/mL) [Decreased Susceptibility: ≥2 μg/mL][a]	Ceftriaxone MIC (μg/mL) [Decreased Susceptibility: ≥0.125 μg/mL][a]	Cefixime MIC (μg/mL) [Decreased Susceptibility: ≥0.25 μg/mL][a]	Penicillin MIC (μg/mL) by Agar Dilution [Resistance: ≥2.0 μg/mL][a]	Tetracycline MIC (μg/mL) by Agar Dilution [Resistance: ≥2.0 μg/mL][a]	Gentamicin MIC (μg/ mL) by Agar Dilution, No Established Interpretive Criteria[a]	Ciprofloxacin MIC (μg/mL) by Agar Dilution [Resistance: ≥1.0 μg/mL][a]
1	Urine	Positive	>16 (agar dilution); >256 (Etest)	0.125 (agar dilution); 0.125 (Etest)	0.125 (agar dilution); 0.125[b] (Etest)	>64	2	8	16
2	Urethra	Positive	>16 (agar dilution); >256 (Etest)	0.125 (agar dilution); 0.125 (Etest)	0.125 (agar dilution); 0.125[b] (Etest)	>64	2	8	16
3	Cervix	Positive	>16 (agar dilution); >256 (Etest)	0.125 (agar dilution); 0.25[b] (Etest)	0.06 (agar dilution); 0.25[b] (Etest)	>64	2	8	16
4a	Urethra	Positive	>16 (agar dilution); >256 (Etest)	0.03 (agar dilution); 0.125[b] (Etest)	0.06 (agar dilution); 0.125[b] (Etest)	>64	2	4	16
4b	Urine	Positive	>16 (agar dilution); >256 (Etest)	0.125 (agar dilution); 0.125 (Etest)	0.125 (agar dilution); 0.125 (Etest)	>64	2	8	16
5	Urethra	Positive	>16 (agar dilution); >256 (Etest)	0.06 (agar dilution); 0.125[b] (Etest)	0.06 (agar dilution); 0.125[b] (Etest)	>64	2	4	8
6	Urethra	Positive	>16 (agar dilution); >256 (Etest)	0.06 (agar dilution); 0.125 (Etest)	0.06 (agar dilution); 0.125 (Etest)	>64	2	4	16
7	Urethra	Positive	>16 (agar dilution); >256 (Etest)	0.125 (agar dilution); 0.125 (Etest)	0.125 (agar dilution); 0.125[b] (Etest)	>64	4	8	16

Etest results and β-lactamase testing were performed at Hawaii Department of Health State Laboratory; agar dilution assays and confirmatory azithromycin Etest were performed at the University of Washington (UW) and Centers for Disease Control and Prevention (CDC) laboratories. Agar dilution MIC results from UW and CDC laboratories were the same or within ±1 doubling dilution.

Abbreviation: MIC, minimum inhibitory concentration.

[a] Interpretive criteria for ciprofloxacin, penicillin, and tetracycline were in accordance with the Clinical and Laboratory Standards Institute [18]. The Gonococcal Isolate Surveillance Project's surveillance definition of reduced susceptibility was used to interpret the MIC values for azithromycin, cefixime, and ceftriaxone [14]. There are no established interpretive criteria for gentamicin.

[b] Etest MIC value fell between standard 2-fold dilutions. It has been rounded up to the next upper 2-fold value for interpretive purposes, as recommended by the manufacturer [19].

Table 2.

Patient Summary: Cluster of *Neisseria gonorrhoeae* Isolates With High-level Azithromycin Resistance and Decreased Susceptibility to Ceftriaxone, Hawaii, April 2016–May 2016

Patient Number	Demographics	Healthcare Setting	Symptoms	Collection Date	Treatment	Clinical Outcome	Post-treatment Test Results Date	Partners
1	56-year-old Asian male	Private	Dysuria	4/21/16	Azithromycin 2 g orally + doxycycline 100 mg orally twice daily × 14 d; retreated with ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Negative, 5/20/16	1 partner: sex worker, not locatable
2	35-year-old Asian male	HDOH STD clinic	Penile discharge	4/25/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Negative, 5/17/16	1 partner: sex worker (massage parlor); same partner named by patient 7, located, examined, and treated at HDOH STD clinic; asymptomatic, negative test results
3	28-year-old Asian female (presented as gonorrhea contact)	HDOH STD clinic	Vaginal discharge	4/28/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms decreased after treatment; pelvic examination post-treatment at HDOH STD clinic noted to be unremarkable	Negative, 5/19/16	2 partners: partner 1 treated for gonorrhea at private clinic 4/25/16 (history of contact with sex worker); repeat test by HDOH: negative. Partner 2 asymptomatic; treated at HDOH STD clinic; negative test results
4	24-year-old Pacific Islander male	Private	Dysuria and penile discharge	4/29/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Negative, 5/31/16	1 partner: lives in Japan; reportedly had negative urine test for gonorrhea in Japan
5	36-year-old Asian male	HDOH STD clinic	Dysuria and penile discharge	5/3/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Negative, 5/31/16	1 partner: identified and records tracked by HDOH disease intervention specialist; tested negative with urine nucleic acid amplification test at community health center
6	47-year-old Caucasian male	HDOH STD clinic	Penile discharge	5/4/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Refused retest	1 partner: not locatable
7	28-year-old Asian male	HDOH STD clinic	Penile discharge	5/10/16	Ceftriaxone 250 mg IM + azithromycin 1 g orally	Symptoms resolved after treatment	Negative, 6/3/16	2 partners: both sex workers from 2 massage parlors; one partner identical to that named by patient 2

Abbreviations: HDOH, Hawaii Department of Health; IM, intramuscular; STD, sexually transmitted disease.