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Fluoroquinolone-Resistant Neisseria gonorrhoeae *in Bali, Indonesia: 2004*

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Objectives: **In the mid-1990s, fluoroquinolones were introduced in Indonesia for the management of gonorrhea and are now part of the national recommended treatment guidelines. We recently documented introduction of ciprofloxacin-resistant *Neisseria gonorrhoeae* strains in female sex workers (FSWs) in Timika, Indonesia, 5 years after treating gonococcal cervicitis with ciprofloxacin and periodically monitoring antimicrobial susceptibility of isolates. To assess the importance of this observation, we determined antimicrobial susceptibilities and strain types of *N. gonorrhoeae* isolates from FSWs seen in a sexually transmitted infection (STI) clinic in Denpasar, Bali, Indonesia.**

Goal: **The goal of this study was to determine antimicrobial susceptibilities and strain types among *N. gonorrhoeae* isolated from FSWs in Denpasar, Bali.**

Study Design: **FSWs in Denpasar were screened for *N. gonorrhoeae* by standard culture. Endocervical isolates were frozen in Microbank tubes and sent to the University of California at San Francisco on dry ice. Antimicrobial susceptibility testing using a Clinical Laboratory Standards Institute-recommended agar dilution method was performed at the Centers for Disease Control and Prevention. Isolates were characterized by β-lactamase production, antimicrobial resistance phenotypes, and auxotype/serovar class.**

Results: **One hundred forty-seven *N. gonorrhoeae* isolates were characterized. All isolates were highly resistant to tetracycline (minimum inhibitory concentration, ≥16.0 μg/mL): 117 (79.1%) were β-lactamase-positive (PP-TR), 3 (2.0%) exhibited chromosomally mediated resistance to penicillin (PenR-TRNG), and 27 (18.2%) were susceptible to penicillin (TRNG). All isolates were susceptible to ceftriaxone, cefixime, and spectinomycin; lack of interpretive criteria do not allow interpretation of susceptibilities of cefoxitin, cefpodoxime, or azithromycin. Fifty-nine (40.1%) isolates were ciprofloxacin-resistant; 35 (59.3%) of the ciprofloxacin-resistant isolates exhibited high-level resistance to ciprofloxacin (Cip-HLR; minimum inhibitory concentration, ≥4.0 μg/mL of ciprofloxacin). Three (2.0%) isolates were intermediate to ciprofloxacin. Twenty-two strain types were identified among these isolates; small clusters were identified with 3 strain types.**

Conclusions: ***N. gonorrhoeae* isolates from FSWs in Denpasar were resistant to penicillin and tetracycline; 40.1% of the isolates were fluoroquinolone-resistant. With gonorrhea prevalence of 35% at this clinic (by nucleic acid amplified tests), ongoing surveillance for antimicrobial resistance will be needed to appropriately choose treatment for infections caused by these resistant organisms.**

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FLUOROQUINOLONES ARE AMONG THE MOST effective antimicrobial agents for the treatment of gonorrhea. Ciprofloxacin is an attractive treatment option because it is inexpensive and can be used for witnessed single-dose oral treatment. However, ciprofloxacin-resistant strains have been reported in many countries. In Asia and the Western Pacific, 10% to 65% of *Neisseria gonorrhoeae* isolates tested are fluoroquinolone-resistant.[1–8] Despite the rapid spread of fluoroquinolone-resistant gonococci throughout this region, information on antimicrobial resistance in *N. gonorrhoeae* in Indonesia is limited. In the mid-1990s, fluoroquinolones were introduced in Indonesia for the management of gonorrhea and are now part of the national recommended treatment guidelines.[9]

In the few antimicrobial susceptibility surveillance studies reported from Surabaya, Bandung, Jakarta, and North Sumatra thus far, resistance to penicillin and tetracycline was widespread, but no fluoroquinolone resistance was detected.[10–14] One report on susceptibilities of gonococci isolated from female sex workers (FSWs) in North Jakarta in 1996 found that 3.3% (4 of 122) of isolates exhibited minimum inhibitory concentrations (MICs) of 0.5 μg/mL for norfloxacin,[13] consistent with intermediate resistance to norfloxacin,[15] but no information on susceptibilities to fluoroquinolones such as ciprofloxacin was reported. A 2001 Australian report correlating quinolone susceptibility with strain changes in the amino acid alteration patterns in GyrA and ParC included one ciprofloxacin-resistant strain isolated and tested in Australia but which had been acquired in Bali, Indonesia, in 1995.[16]

Beginning in January 1997 through 2002, we monitored antimicrobial susceptibility of gonococcal isolates from the sexually transmitted infection (STI) clinic in Timika, West Papua, Indonesia. During this time period, most strains exhibited plasmid-mediated resistance to penicillin and/or tetracycline but, until 2002, were highly susceptible to ciprofloxacin. In 2002, we documented fluoroquinolone-resistant gonococcal isolates in Timika among clinic isolates.[17] Subsequently, 43 of 72 (60%) isolates from that clinic and 45 of 94 (48%) isolates from an STI clinic in Surabaya, Java, were reported to be ciprofloxacin-resistant (Sutrisna A, Soebjakto O, Wignall FS, et al. 9th IUSTI World Congress, 2005: Abstract SS05).

Periodic monitoring of antimicrobial susceptibilities of *N. gonorrhoeae* in high-risk populations gives essential information about changing patterns of drug resistance. In addition, phenotypic or genotypic characterization of resistant strains provides informa-

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tion regarding the diversity of resistant strain populations—the importation and clonal spread of a single strain or the importation of multiple strains. To assess the degree of this resistance, gonococcal isolates from FSWs seen in an STI clinic in Denpasar, Bali, Indonesia, were tested for antimicrobial susceptibility and ciprofloxacin-resistant strains were further characterized.

Materials and Methods

Population

From August to November 2004, consecutive self-identified FSWs from each of 6 different brothels were seen in an STI clinic in Denpasar, Bali, Indonesia. *N. gonorrhoeae* was isolated from 157 individual FSWs; 147 isolates were available for characterization.

Culture Isolation

We used cotton swabs to collect endocervical specimens. These swabs were immediately streaked onto modified Thayer Martin medium. Plates were incubated in candle jars at 36°C for 48 hours. Presumptive gonococcal isolates (oxidase-positive, Gram-negative diplococci) were subcultured onto chocolate agar, frozen in Microbank tubes (Pro-Lab Diagnostic, Austin, TX), and shipped on dry ice to the University of California at San Francisco. Random isolates were subcultured and identified using the Gonochek II test (EY Laboratories, San Mateo, CA).

Antimicrobial Susceptibilities

Gonococcal isolates were sent to the Centers for Disease Control and Prevention (CDC, Atlanta, GA). MICs were determined on BD Difco chocolate agar base containing 1% IsoVitaleX (Becton Dickinson, Sparks, MD) inoculated with 10^4 colony-forming units as recommended by the Clinical Laboratory Standards Institute (CLSI, formally NCCLS).[18] Susceptibilities were determined to penicillin, tetracycline, spectinomycin, ceftriaxone, cefoxitin, cefixime, cefpodoxime, ciprofloxacin, ofloxacin, and azithromycin. Gonococcal quality control strains ATCC 49,226, F-28, CDC 10,328, CDC 10,329, SPL-4, and SPJ-15 were included with each run. Susceptibilities to all agents except cefoxitin, cefpodoxime, and azithromycin were interpreted with CLSI-recommended criteria.[18] A critical MIC of 1.0 μg/mL was used to interpret MICs of azithromycin to indicate resistance when an infection is treated with a single, oral, 2-g dose of this agent. β-lactamase production was detected by the Nitrocefin test (Cefinase; Becton Dickinson). Antimicrobial resistance phenotypes were defined for each isolate as follows: PP-TR, β-lactamase-producing strains with tetracycline MIC, $\geq$16.0 μg/mL (presumptive for the TetM-conjugative plasmid); TRNG, strains with tetracycline MIC, $\geq$16.0 μg/mL; PenR, chromosomally mediated resistance to penicillin (β-lactamase-negative; MIC, $\geq$2.0 μg/mL); CipI, strains with an MIC, 0.125 to 0.5 μg/mL of ciprofloxacin; CipR, strain with MIC, $\geq$1.0 μg/mL of ciprofloxacin; and Cip-HLR, ciprofloxacin-resistant isolates exhibiting an MIC, $\geq$4.0 μg/mL of ciprofloxacin.

Strain Typing

Ciprofloxacin-resistant isolates were characterized by auxotype and a modified serologic classification as described previously but using IA-specific monoclonal antibody reagents 4G5, 2F12, 6D9, 5G9, 5D1, and 9D2 and IB-specific monoclonal antibody reagents 3C8, 2H7, 2G2, and 2D4.[19–21] Monoclonal antibody classification was designated using the IA or IB prefix followed by the pattern of reaction with specific monoclonal antibody reagents. This classification differs from the original classification system as a result of the nonavailability of IA-specific reagent 4A12 and IB-specific reagents 2F12, 2D6, 2D4, and 2HI but with the addition of IA-specific reagent 9D2 and IB-specific reagent 2H7.[20,21]

Results

All 147 gonococcal isolates from FSWs in Denpasar exhibited presumptive plasmid-mediated resistance to tetracycline; 117 (79.1%) produced β-lactamase (PP-TR), 3 (2.0%) exhibited chromosomal resistance to penicillin (PenR-TRNG), and 27 (18.2%) were susceptible to penicillin (TRNG). All isolates were susceptible to ceftriaxone, cefixime, spectinomycin, and azithromycin (Table 1).

A total of 62 (42.4%) of these 147 isolates were intermediate or resistant to ciprofloxacin. A total of 59 (40.1%) were ciprofloxacin-resistant; 35 (59.3%) of the ciprofloxacin-resistant isolates exhibited high-level resistance to ciprofloxacin (Cip-HLR; MIC, $\geq$4.0 μg/mL of ciprofloxacin). Three (2.0%) isolates were intermediate to ciprofloxacin. In Table 2, the distribution of gonococcal isolates is shown by ciprofloxacin resistance category and then by penicillin-tetracycline resistance category and auxotype/serovar class.

A total of 22 auxotype/serovar classes were identified among these isolates. Three clusters—PP-TR/Cip-HLR/Proto/IB-2H7 (4 isolates), PP-TR/Cip-HLR/Proto/IA-4G5,2F12,9D2 (6 isolates), and PP-TR/CipR/Proto/IA-4G5,2F12,9D2 (4 isolates)—were identified among these isolates.

TABLE 1. Antimicrobial Susceptibility of *Neisseria gonorrhoeae* Isolates From Bali (n = 147)

	Minimum Inhibitory Concentration (μg/mL): No. of Isolates																		
Agent	0.002	0.004	0.008	0.013	0.016	0.032	0.064	0.128	0.256	0.512	1	2	4	8	16	32	>32	64	>64	128
Penicillin								1	6	12	8	5	5	6	18	55		19	12	
Tetracycline															18	106	23			
Spectinomycin																				147
Ceftriaxone	11	61	48		26	1														
Cefoxitin										36	81	26	4							
Cefixime		2	67		75	3														
Ciprofloxacin	1	69	8		7			1	2		1	23	27	5	2	1				
Ofloxacin	1	1	21		51	12			1	1		5	36	12	4	2				
Cefpodoxime		3	24		66	27	26	1												
Azithromycin				1			4	50	58	34										

TABLE 2. Distribution of Gonococcal Isolates Intermediate to Ciprofloxacin (Cip) or Exhibiting Resistance or High-Level Resistance to Ciprofloxacin by Ciprofloxacin Resistance Category, Penicillin–Tetracycline (Pen-Tet) Resistance Category, and Auxotype/Serovar Class

	Cip Resistance Category (Pen-Tet Resistance Phenotype [No.])						
	Cip-HLR (35)			CipR (24)		CipI (3)	
Auxotype/Serovar Class	PP-TR (27)	TRNG (6)	PenR, TRNG (2)	PP-TR (19)	TRNG (5)	PP-TR (2)	TRNG (1)
Arg/IA-4G5				1			
Arg/IA-4G5,2F12,5D1,9D2				1			
Arg/IB-3C8	1						
Arg/IB-2H7	1						
Arg/ IB-2H7,2G2	1			1			
Arg/NT	2			1			
PA/IA-4G5,2F12,5D1,9D2						1	
PA/IA-4G5,6D9,9D2						1	
Pro/IA-4G5,2F12,9D2				2			
Pro/IA-4G5,2F12,5D1,9D2				2			
Pro/IB-3C8	1		1				
Pro/IB-3C8,2H7					1		
Pro/IB-2H7	1	1		2	2		
Pro/IB-2H7,2G2	1	1		1			
Pro/NT		2	1		1		
Proto/IA-4G5	1						
Proto/IA-4G5,9D2	2			1			
Proto/IA-4G5,2F12,9D2	6			4	1		1
Proto/IA-4G5,2F12,5D1,9D2	2			1			
Proto/IB-2H7	4			1			
Proto/IB-2H7,2G2		1					
Proto/NT	4	1		1			

Arg indicates arginine-requiring; Pro = proline-requiring; PA = requiring proline and arginine; Proto = no requirement for proline, arginine, hypoxanthine, uracil, or methionine; IA = reacts with protein IA-specific monoclonal antibody reagents; IB = reacts with protein IB-specific monoclonal antibody reagents; NT = nontypeable; PP-TR = β-lactamase-producing strains with MIC $\geq$16.0 μg/mL of tetracycline (presumptive for the TetM-conjugative plasmid); TRNG = strains with MIC $\geq$16.0 μg/mL of tetracycline (presumptive for the TetM-conjugative plasmid); PenR = chromosomally mediated resistance to penicillin (β-lactamase-negative with an MIC $\geq$2.0 μg/mL of penicillin); CipI = strain with MIC 0.125–0.5 μg/mL of ciprofloxacin; CipR = strain with an MIC $\geq$1.0 and $<$4.0 μg/mL of ciprofloxacin; Cip-HLR = ciprofloxacin-resistant isolates exhibiting MIC $\geq$4.0 μg/mL of ciprofloxacin; MIC = minimum inhibitory concentration.

Discussion

We documented ciprofloxacin resistance in 40.1% of *N. gonorrhoeae* isolates from FSWs in Denpasar, Bali, in 2004. The frequency of detection of ciprofloxacin-resistant strains in Denpasar is similar to the detection of ciprofloxacin resistance in 48% of isolates from FSWs in Surabaya, Java, and 60% in Papua in 2004. These frequencies represent a significant level of resistance among FSWs and probably other individuals with gonococcal infection in these cities.

Ciprofloxacin-resistant gonococci may also be prevalent but unrecognized in other areas of Indonesia as a result of lack of surveillance given the mobility of FSWs who often work for only 3 to 6 months in one location and the mobility of their Indonesian clients, many of whom work on "single status" in one area and maintain families in a different area of Indonesia. The current prevalence of ciprofloxacin resistance over the country is unknown because gonococcal antimicrobial susceptibility testing is not routine in Indonesia.

The ciprofloxacin-resistant isolates identified in Denpasar included clusters of isolates belonging to the same strain type, which may represent endemic spread of some strains as well as a larger number of strain types, each represented by one or few isolates, which probably represent the sporadic isolation of most strains as defined by auxotype/serovar class and antibiograms. The frequency of ciprofloxacin resistance and the diversity in auxotype/serovar and penicillin–tetracycline resistance phenotypes among the strains examined here may be explained in several ways. Ciprofloxacin-resistant gonococcal isolates may have been present in Bali since 1995 when an isolate was detected.[16] A multiplicity of resistant strains may have been imported by travelers to Bali from other areas of Asia where ciprofloxacin resistance has been reported for some time or from other cities in Indonesia where resistance has not been recognized. Alternatively, the strain diversity present in Bali may also suggest the possibility of a sustained but poorly recognized domestic transmission of ciprofloxacin-resistant *N. gonorrhoeae* in Bali over the last decade as evidenced by the isolation of resistant strains in Australia from travelers who were thought to have acquired infection in Indonesia. However, because there are little data on either the frequency or strain diversity of ciprofloxacin-resistant isolates in Indonesia, and in Bali in particular between 1995 and 2004, it is difficult to interpret the significance of the sporadic available reports. Local selection of resistant strains could have occurred based on self-medication by sex workers, suboptimal therapy, or reexposure to *N. gonorrhoeae* after single-dose treatment when a suboptimal concentration of drug was present. However, surveillance of gonococcal isolates intermediate to ciprofloxacin in Ohio failed to observe the "emergence" of ciprofloxacin-resistant strains from the intermediate strains during a prolonged period of time, suggesting that de novo selection of ciprofloxacin-resistant strains is a rare event.[22]

Both rapid and slower rates of fluoroquinolone-resistant *N. gonorrhoeae* spread in communities are reported.[23–25] Slower rates

are thought by some to occur when resistant strains (many strain types) are imported, whereas a decrease in types of resistant strains occurs when endemic spread replaces importation.[26] The spread of fluoroquinolone resistance in Bali may be similar to that seen in Hawaii in the 1990s. In Hawaii, there were sporadic reports of ciprofloxacin-resistant gonococci beginning in 1991 until the late 1990s when a sudden increase in the frequency of resistant isolates was noted.[27] During this time period, the diversity of strain types indicated that resistant strain types were imported and eradicated. It was not until the late 1990s that, concurrent with the increased frequency of isolation of resistant strains, the profile of strain types was characterized by larger numbers of isolates belonging to one or 2 strain types—indicative of endemic spread—and fewer strain types represented by only one or 2 isolates.[27] It is quite probable, had a similar, long-term surveillance of ciprofloxacin-resistant isolates been conducted in Denpasar, that a similar strain profile might have been observed.

The presence of 3 clusters based on penicillin–tetracycline resistance phenotype, ciprofloxacin resistance category, and auxotype/serovar class supports the endemic spread of these isolates in Denpasar. Further examination of endemic spread of ciprofloxacin-resistant strains in Denpasar would require a detailed investigation to identify epidemiologically linked isolates together with discriminatory typing systems such as NG-MAST.[28]

Presently, ciprofloxacin is the most widely used antimicrobial agent recommended in national guidelines for treating uncomplicated gonococcal infections in Indonesia. Alternate effective oral, single-dose agents such as cefixime are much more costly and the number of FSWs, all of whom merit treatment, is also high. The number of Indonesian FSWs is estimated to be as many as 273,000,[29] and 35% to 60% are infected with gonorrhea when amplified nucleic acid testing is used for detection.[30,31]

At the moment, no cost-effective, single-dose, oral therapy other than ciprofloxacin is available in Indonesia. Ideally, single-dose oral treatments such as cefixime or cefpodoxime should be used in areas with greater than 5% ciprofloxacin resistance. World Health Organization guidelines for surveillance of antimicrobial susceptibility and development of national standards suggest that alternative treatments should be included in national recommendations for areas with greater than 5% resistance.[32,33] Alternatively, treatment of ciprofloxacin-resistant uncomplicated gonococcal infections will require intramuscular injection with either kanamycin or spectinomycin provided that single-use needles can be made available to ensure the administration of sterile injections. Kanamycin is readily available, inexpensive, and used for the treatment of gonococcal cervicitis in Indonesia. However, the cure rate after intramuscular injection of kanamycin is less than ideal. Lim, in 2 studies involving men with gonococcal urethritis/cervicitis, reported a cure rates of 83.3% (20 of 24 men), 92.7% (16 of 19 men), and 96% (48 of 50 women) for infections with penicillinase-producing gonococci (PPNG) and 88.7% (63 of 71 men) and 83.3% (25 of 30 men) for non-PPNG gonococci.[34,35] In Zambia, a 95% cure rate in 113 men with urethritis treated with 2 g kanamycin is reported.[36]

The choice of treatment should be based on continued local surveillance of antimicrobial susceptibilities. A national program of ongoing antimicrobial susceptibility testing should be initiated in Indonesia at sentinel sites to inform treatment programs. The World Health Organization has developed surveillance standards for antimicrobial resistance, which include the required sample sizes needed to validly obtain resistance rates.[32] In the meantime, medical personnel and dispensing pharmacists treating patients with gonorrhea will need to be alerted to the potential for ciprofloxacin resistance in *N. gonorrhoeae*.

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