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Antimicrobial Resistant Gonorrhea in Atlanta: 1988 – 2006

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Abstract

Gonococcal isolates (n = 4336) were collected from men with urethritis at the Fulton County STD Clinic from 1988 – 2006. Antimicrobial susceptibility was performed by agar dilution. Increasing numbers of isolates from MSM and with fluoroquinolone resistance were noted. New antimicrobials effective against gonorrhea are urgently needed.

Keywords

gonorrhea; fluoroquinolone resistance (QRNG); GISP; Atlanta

Gonorrhea is the second most commonly reported sexually transmitted disease (STD) in the United States. According to the 2008 STD Surveillance data from CDC, the rate for gonorrhea in the US was 112 cases per 100,000 population. Although rates over the past ten years have been generally stable, geographically, the South has always had the highest gonorrhea rates in the country. In 2008, the state of Georgia had the 6th highest case rate for gonorrhea nationwide (171 cases/100,000 population). Fulton County, which includes most of Atlanta, had a rate of 297 cases/100,000 population [1].

National monitoring of antimicrobial resistance in *Neisseria gonorrhoeae* in the United States has been possible since 1986 under the auspices of the CDC sponsored Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance project conducted at 25–30 sites. It was established to monitor trends in antimicrobial susceptibility of gonococcal isolates from men with urethritis and described elsewhere [2]. Details of laboratory procedures and data collection can be accessed online at www.cdc.gov/std/gisp as well as in the CDC GISP annual report [3]. The emergence of fluoroquinolone resistance (QRNG) in the US, as documented by GISP, has been reviewed by Fox et al (1988–1994), and Wang et al (1988–2003) [4–6].

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The purpose of the current analysis is to document antimicrobial resistance in *N. gonorrhoeae*, demographic characteristics and describe the trends in antibiotics used to treat gonococcal urethral infections at the Fulton County Department of Health and Wellness (FCDHW) STD Clinic from 1988–2006.

Linear regression was used to assess the trend of age over time and Kruskal-Wallis test was used for the association of age with QRNG. To test the trend of MSM as a categorical variable over time, the Cochran-Armitage test was used. Chi-squared test was used to look for an association between QRNG and age (dichotomized as younger than 30 or 30 and older). Geometric mean was calculated for each year of MIC data for azithromycin. Data analyses were performed using SAS Enterprise Guide 4.

Antimicrobial susceptibilities were determined for all samples by the Emory University GISP regional laboratory using agar dilution methods and MICs were interpreted according to the most recent Clinical Laboratory Standards Institute (CLSI) breakpoints published in January 2007 [7]. Ciprofloxacin resistance is defined as MIC ≥ 1 μg/mL with intermediate resistance at MIC 0.125–0.5 μg/ml. There are no CLSI guidelines that define azithromycin susceptibility or resistance, but criteria from the GISP protocol lists the decreased susceptibility cutoff at MIC ≥1 μg/mL. In 2005, this cutoff for decreased susceptibility was changed to ≥ 2 μg/mL due to a change in media. [8]

There were 4,336 isolates collected from 1988–2006 for the FCDHW STD Clinic as part of GISP. Patient characteristics are listed in Table 1. Men who reported only having sex with men increased significantly over the study period from 1% in 1996 to 9% in 2006 (p=0.0001). The percent that were bisexual also increased from 0.5% in 1996 to 3.7% in 2006 (p=0.02) (Figure 1 shows homosexual and bisexual rates combined as MSM rates). Data on HIV prevalence has been captured for a subset of GISP Fulton County clients since 2002 and has averaged 4.8% over five years. HIV prevalence was 31% among MSM (26/84), and 1% (9/633) among men who denied having had sex with men. Many patients (35.8% to 60% each year) had a previous history of gonococcal infection and, when stratified by age, this was more common among ages 18–25 relative to older males.

In terms of changing gonorrhea treatment patterns, ampicillin or amoxicillin was prescribed for 89% of patients in 1988, then ceftriaxone for 85% in 1989–1990. From 1991–1994, oral ofloxacin 400 mg was given to most patients (range 48%–84% of treated patients). Since 1996, ceftriaxone 125 mg intramuscular has been the drug of choice for prescribers although the dosage of 250 mg IM was given more frequently from 1998–2001. Fluoroquinolones have been used minimally to treat gonorrhea since 1996, ranging from 0–1.6% of all antibiotics prescribed for gonococcal infections. Spectinomycin has not been given since 2001. Only fifteen patients of this group received two grams of azithromycin and one patient received doxycycline as gonorrhea therapy between 2002 and 2006.

There were 25 cases of QRNG documented from 1988–2006, insufficient cases for an analysis of risk factors based on sexual orientation or HIV status. Among the clients with QRNG, 28% reported having sex with men and 4% were HIV infected. There was sufficient data to consider age as a risk factor for QRNG, but there was no association noted. Intermediate resistance to ciprofloxacin was first noted in an isolate from 1997, it peaked at 5.3% in 1999 and then disappeared after 2002. In 1997, and again in 2004, one isolate was noted to have high level resistance to ciprofloxacin (MIC 1 μg/ml and MIC 2 μg/ml, respectively). QRNG prevalence subsequently increased to 3.8% in 2005 and 5.7% in 2006. (Figure 2) In 2006, 36% of the QRNG had an MIC 16 μg/ml or greater.

Azithromycin has been included in the panel of antibiotics tested since 1997. Among the isolates tested, decreased susceptibility was first noted in two isolates during 2000. By 2004,

6% (7/116) of isolates tested had decreased azithromycin susceptibility (MIC 1–4 μg/ml) (Fig 3). Presence of β-lactamase in sampled *N. gonorrhoeae* isolates peaked in 1990 and has been stable at minimal levels since 2003 (range 0.4–1.2%). Similarly, resistance to penicillin has been present at levels ranging from 1–8% over the past five years. Chromosomally mediated resistance to tetracycline (MIC 2–8 μg/ml) peaked at 41% in 1995 and now ranges from 4–11% while the plasmid mediated high level resistance (MIC ≥16 μg/ml) peaked later (18% in 1998) and is seen in approximately 5% of samples from 2004–2006. There is no documented resistance to spectinomycin from 1988–2006. For the cephalosporins, there have been no isolates with documented resistance to ceftriaxone during the study period, although a single isolate had decreased susceptibility to cefixime in 1992 (MIC 0.5 μg/ml).

This sentinel surveillance data from Fulton County shows the rapid introduction and spread of fluoroquinolone resistance and increases in azithromycin geometric mean titers since 1997. Age was not associated with QRNG but MSM were more likely to have QRNG than heterosexual men although the total number of QRNG cases was small and did not permit statistical analysis. This association of MSM with QRNG has been shown in previous studies [9]. There are a wide variety of reported QRNG rates nationally, from 23% in Los Angeles, 44% in San Francisco, 4.1% in Chicago and 1.4% in Baltimore [10]. Reports of case clusters of GC with decreased susceptibility to azithromycin are concerning (33 cases were reported in Kansas City from 1999–2000) and national GISP data from 2003–2006 also shows increasing MICs for azithromycin.[10, 11].

In the absence of fluoroquinolones, there had been no available oral treatment options for uncomplicated urogenital gonococcal infections until April 2008, when cefixime (400 mg PO) once again became available [12]. Newly updated 2010 STD Treatment Guidelines recommend ceftriaxone 250 mg intramuscular in addition to azithromycin 1 gram orally or oral doxycycline 100 mg twice daily for seven days to treat uncomplicated gonorrhea infection. [13] Sporadic *Neisseria gonorrhoeae* isolates with decreased susceptibility to cefixime, ceftriaxone, and azithromycin have been reported and reports of clinical failure are increasing [11, 13, 14].

Gonorrhea is a commonly reported infection in Fulton County and rates in the South have always been the highest in the nation [3, 15]. The fact that 4.8% have HIV infection and 6–18% had prior episodes of gonorrhea suggest ongoing high risk behaviors among this population. These findings are similar to a study of HIV testing in Atlanta that included 1,495 FCHD patients and documented 1.9% HIV prevalence [16]. In addition, the percentage of self-reported MSM has drastically increased from 1% to 13% for the Fulton County GISP subset from 1996–2006. Further efforts are needed to prevent sexually transmitted infections among MSM.

Limitations of the study include generalizability of the findings to women (since only males participate in GISP) and persons who may have less risky sexual practices. Findings may not be representative of all patients with gonorrhea in Fulton County, other STD clinics, or other GISP sites. Insufficient data were collected on individual and community level antibiotic usage to account for its contribution to resistance patterns. Collection of sexual orientation data is limited by reporting bias and HIV status information has only been collected since 2002.

Gonorrhea continues to challenge our public health system in its persistence and increasing antimicrobial resistance profile. The ability to identify antimicrobial resistance in isolates of *N. gonorrheae* is increasingly problematic since most clinical laboratories now rely on non-culture based methods for diagnosis which do not allow for antimicrobial susceptibility testing. Cephalosporins remain the recommended treatment, but newer therapies are

urgently needed in light of recent reports of decreased susceptibility to cefixime and treatment failures as well as increased MIC's for azithromycin. Providers should have a high suspicion for potential treatment failure after treatment of gonorrhea and these cases should be brought to the attention of local health authorities so that suspicious isolates can be further investigated and antimicrobial susceptibility testing performed.

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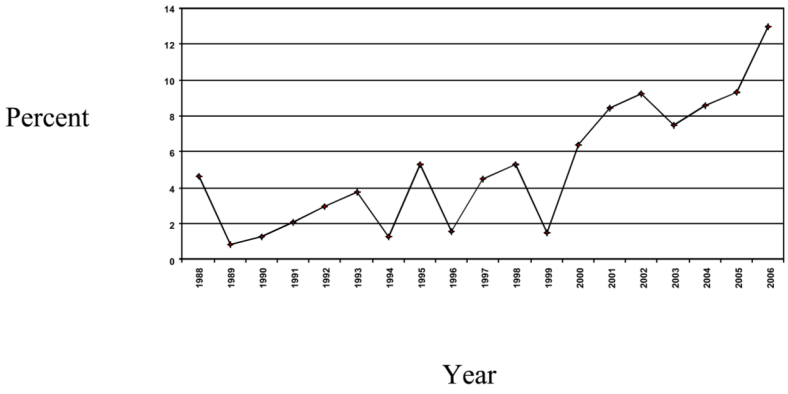

Figure 1. Percent of isolates obtained from men who report sex with men (MSM[1]) in GISP FCDHW[2], 1988–2006

[1]MSM = men self identifying as homosexual or bisexual

[2] FCDHW = Fulton County Department of Health and Wellness

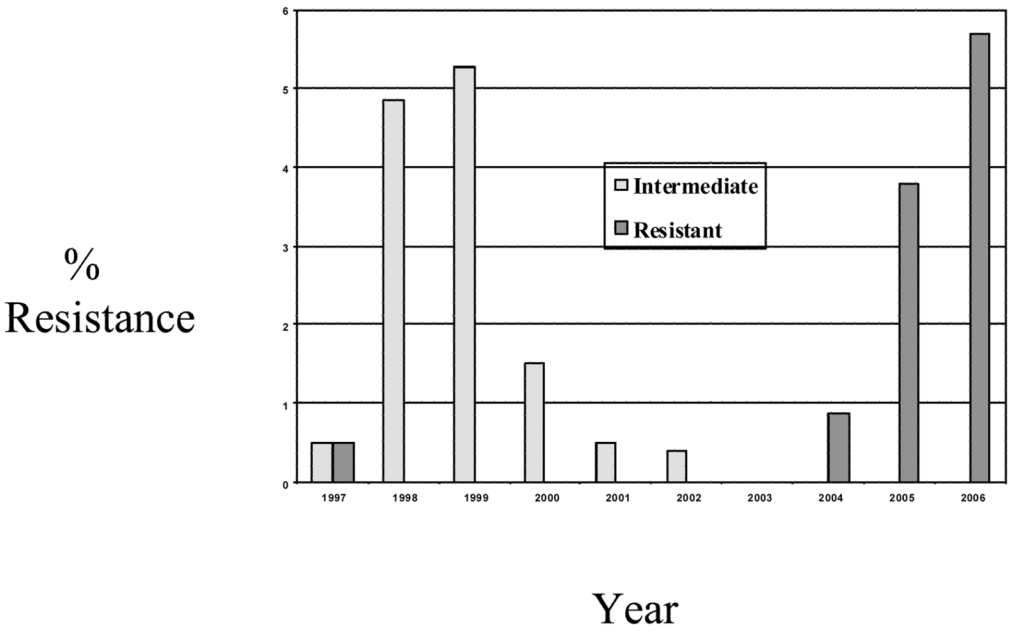

Figure 2. Intermediate susceptibility and resistance to ciprofloxacin in isolates from FCDHW[1] in GISP, 1997–2006

Note: Intermediate susceptibility is defined as MIC 0.125–0.5 μg/ml

Resistance to ciprofloxacin is defined as MIC ≥ 1 μg/ml

[1] FCDHW = Fulton County Department of Health and Wellness

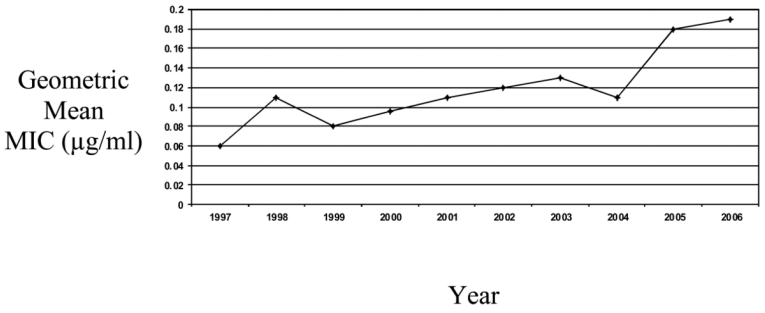

Figure 3. Geometric mean trend of MICs for azithromycin, in GISP, FCDHW[1], 1997–2006

[1] FCDHW = Fulton County Department of Health and Wellness

Table 1

Characteristics of FCDHW[1] Males Sampled by GISP, 1988–2006

	N (%)
Race/Ethnicity (n=4256)	
African-American	4186 (98.3)
White	54 (1.2)
Asian/Pacific Islander	12 (0.3)
Hispanic	4 (0.1)
Age Groups (years) (n=4269)	
10–19	643 (15.1)
20–29	1897 (44.4)
30–39	1043 (24.4)
40+	686 (16.1)
Sexual Orientation (n=4113)	
Heterosexual	3893 (94.6)
Homosexual	135 (3.3)
Bisexual	85 (2.1)
HIV Status* (n=732)	
Positive	35 (4.8)
Negative	687 (93.9)
Indeterminate	10 (1.4)
Reason for Presentation (n=4172)	
Volunteer	4105 (98.4)
Contact	44 (1.0)
Test of Cure	13 (0.3)
Other	10 (0.2)
History of GC (ever) ^ (n=3092)	
Yes	1688 (54.6)
No	1404 (45.4)
Episodes GC past 12 mo† (n=1686)	
0	994 (59.0)
1	297 (17.6)
2–9	395 (23.4)

[1] FCDHW = Fulton County Department of Health and Wellness

* HIV Status – data available for 2002–2006 only. Most current HIV status known at the time of clinic visit for gonorrhea.

^ History of GC – data available after 1991

† Episodes of GC – data available after 1992