

Evaluation of *Neisseria gonorrhoeae* Isolates Susceptibility to Antibiotics in Zhejiang Province Since 2007

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Objective: This study aimed to assess the drug susceptibility of clinical isolates of *Neisseria gonorrhoeae* to spectinomycin, ceftriaxone and azithromycin. Moreover, the temporal trends in the minimum inhibitory concentration (MIC) of five antibiotics from Zhejiang, China, are also in the scope of this study.

Methods: A total of 1710 gonococcal clinical strains were collected between 2007 and 2021 from health-care institutions in Zhejiang. The MICs of ceftriaxone, azithromycin, spectinomycin, penicillin and ciprofloxacin were assessed by agar dilution method on 1710 *Neisseria gonorrhoeae* isolates. Count data were expressed as strains and rates, and MICs distribution was elucidated using descriptive statistics.

Results: The total resistance rates of gonococci to azithromycin, spectinomycin, penicillin and ciprofloxacin in this study were 19.3%, 0.3%, 75.4% and 99.7%, respectively.

Conclusion: The in vitro results showed a high prevalence of resistance to ciprofloxacin and penicillin. Azithromycin resistance rate has exceeded 5%, suggested a high prevalence of resistance. Ceftriaxone and spectinomycin are suggested based on this study for the treatment of *Neisseria gonorrhoeae* in Zhejiang.

Keywords: *Neisseria gonorrhoeae*, agar dilution method, ceftriaxone, spectinomycin

Introduction

Gonorrhea, a sexually transmitted infection (STI) caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), is primarily a purulent infection of the genitourinary system, and patients may present with significant clinical symptoms or present with a subclinical infection or carrier state. According to statistical analysis from the World Health Organization (WHO), there were 87 million new cases of gonorrhea worldwide in 2016,¹ an increase from 78 million in 2012.² According to the Centers for Disease Control and Prevention (CDC), cases of gonorrhea in 2020 were 677,769, and rates of reported gonorrhea have increased 111% since the historic low in 2009 in the United States.³ The incidence of gonorrhea in China fluctuates from 7.36/100,000 in 2015 to 10.06/100,000 in 2017 and back to 8.45/100,000 in 2019, with an overall average annual increase of 3.51%.⁴ In 2021, the number of reported cases of gonorrhea in China was 127,803, ranking fourth in the total number of reported cases of statutory infectious diseases, which makes it the second most common sexually transmitted after syphilis.⁵ At present, antibiotics are still the main means to treat gonorrhea. However, due to the abuse of antibiotics and incomplete monitoring, the sensitivity of *N. gonorrhoeae* to correspondent antibiotics decreases constantly, which has become a serious public health problem.^{6–9}

Undoubtedly, effective and accessible antibacterial treatment is essential for the management of gonorrhea. Yet, *N. gonorrhoeae* has already developed resistance to existing therapeutic drugs, such as sulfonamides, penicillins, tetracyclines, early macrolides and fluoroquinolones. Various factors have contributed to the development and spread of drug-resistant strains, for instance, poor surveillance systems and misuse of antibiotics, antibiotic exposure has been demonstrated to induce tolerance to CRO by *N. gonorrhoeae*.¹⁰ In order to control the development of resistance of strains to the aforementioned antibiotics and prevent complications in Zhejiang. In this study, we determined the drug susceptibility of 1710 gonococcal strains collected between 2007 and 2021 in Zhejiang. Subsequently, the time variation trend of the corresponding minimum inhibitory concentrations (MICs) was discussed to provide a reference for the rational use of antibiotics in the treatment of gonorrhea.

Materials and Methods

Gonococcal Isolates

A total of 1710 gonococcal clinical isolates collected from January 2007 to December 2021 at designated medical and health institutions in Zhejiang (sample sizes per year were 118, 71, 43, 98, 123, 100, 100, 123, 105, 95, 136, 113, 200, 150, 135 respectively) were selected for antimicrobial susceptibility testing. Prior to the antimicrobial susceptibility test, morphological identification and oxidase tests were repeated to identify *N. gonorrhoeae*, which was passed on once and stored in a skimmed milk tube, frozen at -70°C for standby. WHO reference strains J, K, L, P, Y and Z were used for quality control in each batch of tests.

Drug

Spectinomycin, ceftriaxone, azithromycin, ciprofloxacin and penicillin were obtained from United States Pharmacopeia (USP).

Experimental Method

The minimum inhibitory concentration (MIC) of isolates from Zhejiang region against spectinomycin, ceftriaxone, azithromycin, ciprofloxacin and penicillin was determined by agar dilution method in batches. We inoculated the isolated strains from the frozen storage solution to the selective TM medium and then grew the revived strains on the GC agar medium for 18–20 h at 36°C in a 5% CO_2 -enriched and humidified environment, followed by a passage culture. Before conducting antibiotic susceptibility testing, morphological identification and oxidase tests were repeatedly completed. Then, made 1.5×10^8 CFU/mL bacterial solution by scraping the passage culture, completely grinding it, and combining it with sterile normal saline (equivalent to 0.5 McDonnell tube concentration). It should be diluted 1:10 to a concentration of 10^7 CFU/mL before being suspended. Suspensions of 1710 samples were prepared by adding scraped colonies into sterile saline solution (Pengyao Pharmacy, Wuxi, China), and suspensions (10^4 per inoculation) were added to the culture medium (GC agar base medium supplemented with 10% defibrinated sheep blood) containing antibiotics on a square plate using a multipoint inoculator. Next, the plates were incubated at 36°C humidified 5% CO_2 -enriched atmosphere for 18 to 24 h, and the *N. gonorrhoeae* growth in plates containing various antibiotic concentrations was observed and recorded. The breakpoint of antibiotic resistance in this study adopted CLSI standard.¹¹

Statistical Analysis

The results of the batch were recorded if the MIC value of the standard strain was within the standard MIC value or ± 1 concentration of the standard MIC value indicating the validity of this test.¹² If the MIC value of the standard strain was not within the appeal range, it indicates that this test was invalid and the antimicrobial drug pans needed to be reconstituted and measured. The included experimental results were expressed in terms of the number and rate of strains, then calculated descriptive statistics (range, mode, MIC_{50} , MIC_{90}) to characterize the distribution of antibiotic MICs results. Furthermore, the drug sensitivity distribution of clinical gonococcal isolates in Zhejiang was analyzed descriptively. SPSS software 22.0 (SPSS Inc., Chicago, USA) and Excel 2019 (Microsoft, Washington, USA) were applied for data analysis. Figures were made in GraphPad.

Results

Antimicrobial Susceptibility Test of 1710 Isolates

1710 clinical isolates of *N. gonorrhoeae* were tested for antimicrobial susceptibility. CLSI standard was selected as the breakpoint value in this study. The MICs range, mode, MIC₅₀, MIC₉₀ and the percentage of drug-resistant bacteria of gonococci to five antibiotics are shown in Table 1. In this study, the MIC range of ceftriaxone was ≤ 0.008 –4mg/L, MIC₅₀ and MIC₉₀ were 0.03 and 0.06mg/L, respectively. A total of 35 intermediately susceptible strains of ceftriaxone were found, with a total intermediately susceptible rate of 2.05%. The MICs ranges of azithromycin, MIC₅₀ and MIC₉₀ were ≤ 0.03 to >4 , 0.25 and 2 mg/L, respectively, with an overall resistance rate of 19.3%. The MIC₅₀ and MIC₉₀ of spectinomycin were 16 and 32 mg/L, respectively, and a total of 4 resistant strains were found, with an overall resistance rate of 0.3%. The total resistance rates of penicillin and ciprofloxacin were 75.4% and 99.7%, respectively.

Resistance/Hyposensitivity Trend of *N. gonorrhoeae* to Azithromycin, Spectinomycin, Penicillin, Ciprofloxacin and Ceftriaxone

To determine the resistance trend of *N. gonorrhoeae* to different antibiotics in Zhejiang, the temporal MICs trend of five antibiotics was compared (Figure 1). Among them, only three and one ciprofloxacin-sensitive strains were detected in 2007 and 2008, respectively, while the rest of the strains were resistant to ciprofloxacin, indicating that the resistance rate of gonococci to ciprofloxacin in Zhejiang province was maintained at a high level. Overall, 1157 gonococcal strains collected from 2013 to 2021 showed resistance rates to azithromycin in different years of 12.0%, 22.0%, 36.2%, 16.8%, 27.9%, 28.3%, 20.4%, 19.3% and 29.7%, respectively, and the resistance rates of 672 isolates to penicillin in the years 2013–2018 were 53.0%, 76.4%, 78.1%, 83.2%, 72.1% and 78.8%, respectively. Among which, an increasing trend in ceftriaxone hyposensitivity can be observed in this time frame (ceftriaxone MICs ≥ 0.25 mg/L was defined as cephalosporin hyposensitivity (DSC)). In 2008, 2011, 2016, 2017, 2018, 2019, 2020 and 2021, 2, 1, 2, 1, 11, 8, 7 and 3 strains of DSC were detected, respectively. For spectinomycin, only three and one resistant strains were detected in the years 2018 and 2019 (Table 2).

Trend of Dual Resistance/Hyposensitivity of *N. gonorrhoeae* to Azithromycin and Ceftriaxone

Azithromycin is a semi-synthetic macrolide antibiotic that was used early as a treatment for bacterial sexually transmitted infections to treat gonococcal infections. From the monitoring results of azithromycin resistance to *N. gonorrhoeae* in Zhejiang Province from 2013 to 2021, it was shown that azithromycin-resistant *N. gonorrhoeae* fluctuated between 29.0%–74.29% in 1157 clinical strains, and the monitoring data of Zhejiang Province showed that the ratio of azithromycin-resistant strains had an increasing trend, the ratio of azithromycin strains was 29% in 2013, the ratio increased to 42.28% in 2014, and continued to increase to 74.29% in 2015. The clinical strain azithromycin MIC₅₀ isolated in Zhejiang Province also increased from 0.125mg/L in 2013 to 0.5mg/L in 2018, and the MIC₅₀ in 2019 was 0.25mg/L. From 2013 to 2021, a total of 3 clinical strains with hyposensitivity/resistance to ceftriaxone and azithromycin

Table 1 CLSI Standard Drug Resistance Breakpoint and Drug Susceptibility Results of 1710 Clinical Isolates of Gonococcus

Antimicrobial	Drug Sensitivity Test Results (mg/L)				CLSI Standard (mg/L)			Percentage of Resistant Isolates
	MIC Range	Mode	MIC ₅₀	MIC ₉₀	Susceptible	Intermediately Susceptible	Resistant	
Ceftriaxone	≤ 0.008 –4	0.03	0.03	0.06	≤ 0.25	≥ 0.25	–	–
Azithromycin	≤ 0.03 – >4	0.25	0.25	2	≤ 0.25	0.5	≥ 1	19.3%
Spectinomycin	≤ 4 –256	16	16	32	≤ 32	64	≥ 128	0.3%
Penicillin	0.06– >8	>8	>8	>8	≤ 0.06	0.125–1	≥ 2	75.4%
Ciprofloxacin	0.125– >8	>8	>8	>8	≤ 0.06	0.12–0.5	≥ 1	99.7%

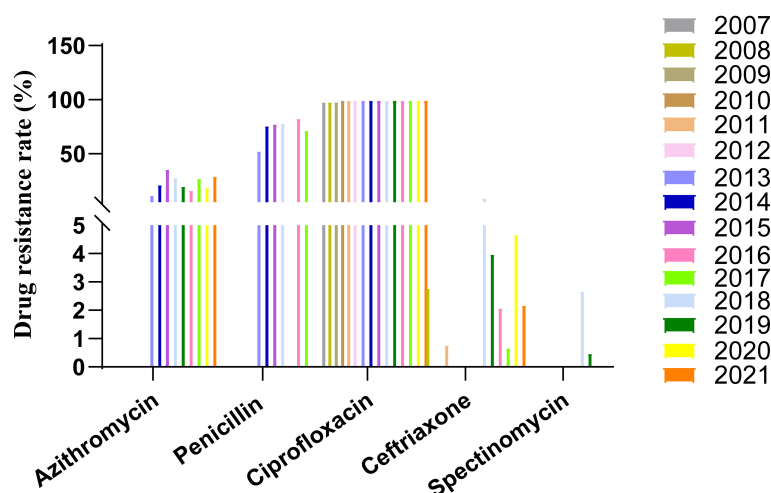


Figure 1 Trend of Drug Resistance/intermediately Susceptible of Gonococci to Five Antibiotics from 2007 to 2021.

resistance were detected in Zhejiang Province, and the emergence of these strains and the growing trend of drug resistance in China will bring great challenges to the treatment effect of gonorrhea.

Discussion

Gonorrhea is extremely common worldwide, with a prevalence of 0.9% in women, and can present with cervicitis or urethritis in women, but most are asymptomatic. If left untreated, gonococcal infections can lead to serious sequelae, including pelvic inflammatory disease, ectopic pregnancy and PID. The proportion of asymptomatic infections in men is low, and epididymitis and prostatitis can be co-infected.¹³ In 2012, WHO published a global action plan and updated

Table 2 Drug Resistance/Intermediately Susceptible of Gonococci to Five Antibiotics from 2007 to 2021

Year	Resistance Rate	Ceftriaxone (%)	Azithromycin (%)	Spectinomycin (%)	Penicillin (%)	Ciprofloxacin (%)
2007		0	NA	0	NA	98.4
2008		2.8	NA	0	NA	98.6
2009		0	NA	0	NA	100
2010		0	NA	0	NA	100
2011		0.8	NA	0	NA	100
2012		0	NA	0	NA	100
2013		0	12	0	53	100
2014		0	22	0	76.4	100
2015		0	36.2	0	78.1	100
2016		2.1	16.8	0	83.2	100
2017		0.7	27.9	0	72.1	100
2018		9.7	28.3	2.7	78.8	100
2019		4	20.4	0.5	NA	100
2020		4.7	19.3	0	NA	100
2021		2.2	29.7	0	NA	100

guidelines regarding gonococcal resistance to regulate the spread of gonococcal infections and minimize the further development of antibiotic resistance. The programs proposed by WHO include “dose escalation”, “new drug development” and “new use of old drugs.” According to WHO treatment guidelines and the United States,¹⁴ Australia,¹⁵ Canada,¹⁶ Europe¹⁷ and other countries, the combination of ceftriaxone and azithromycin is a first-line recommended treatment for gonorrhea. In China, the first treatment option is monotherapy with ceftriaxone or spectinomycin. However, cases of ceftriaxone treatment failure have been incessantly reported from Australia, France, Japan, Norway, Sweden, and the United Kingdom.¹⁸ Along with the development of gonococcal drug resistance, multidrug-resistant clinical isolates continue to emerge, these situations inflict a heavy burden on global medical and health. Consequently, this study was the first to analyze the multi-year trends in antibiotic susceptibility and resistance of *N. gonorrhoeae* in Zhejiang, to explore the appropriate drugs for the treatment of gonorrhea in Zhejiang.

Penicillin is a β -Lactam antibiotics that refer to a class of antibiotics containing penicillanic molecular moiety. It can lead to an abnormal composition of the bacterial cell wall, and hence plays a bactericidal role in the propagation period of bacterial cells. In this study 1225 clinical strains of gonococci collected from 2007 to 2018 were penicillinase-producing *Neisseria gonorrhoeae* (PPNG), which fluctuated between 46.15% and 55.02%. From 2013 to 2015, the ratio of penicillin-resistant strains skyrocketed at first and then flattened. Overall, the drug resistance of *N. gonorrhoeae* isolates to penicillin in Zhejiang province was maintained at a stable high level, so was the detection rate of PPNG. Ciprofloxacin is the third generation of synthetic quinolone antibiotics with broad-spectrum antibacterial activity. Between mid and late 1980s, it was widely used in the treatment of gonorrhea. Initially, *N. gonorrhoeae* was highly sensitive to ciprofloxacin, a low dose ciprofloxacin can provide significant efficacy. Ever since, reports of clinical failure began to surface unceasingly. Among 1282 gonococcal isolates collected in Shenzhen from 2010 to 2017, 68.2% were resistant to penicillin and 97.4% were resistant to ciprofloxacin.¹⁹ Between 2015 and 2017, Siriraj Hospital, Bangkok, Thailand, collected 117 *N. gonorrhoeae* isolates from patients with gonococcal infections, the proportions of isolates with resistance were 84.6% for penicillin, 91.5% for tetracycline, and 96.6% for ciprofloxacin.²⁰ In this study, the monitoring data of *N. gonorrhoeae* drug resistance detection in Zhejiang from 2007 to 2018 showed that only 4 clinical isolates were susceptible to ciprofloxacin, and other samples were resistant to ciprofloxacin. The MIC₅₀ values were all higher than 8 mg/L in 2007–2012, while the values in 2013–2018 were higher than 16 mg/L. This result demonstrates that although ciprofloxacin has long been not recommended for clinical gonorrhea treatment, its drug resistance has not reduced. For about three decades, the fluoroquinolone antibiotic ciprofloxacin has been used to treat urinary tract infections. The main mechanism of fluoroquinolone resistance is mutations in *gyrA* and *parC* genes, which produce one or more specific concurrent mutations in *gyrA* and *ParC* proteins.²¹ These mutations can be easily transferred to other gonococci and spread in the population. Therefore, the resistance rate of ciprofloxacin has remained high for many years.

Ceftriaxone belongs to the third generation of cephalosporins and possesses a satisfactory antibacterial effect on wide range bacteria. It prohibits bacterial growth mainly by inhibiting the synthesis of bacterial cell walls. In this study, the strains from Zhejiang collected between 2007 and 2021 demonstrate ceftriaxone MIC \geq 0.125 mg/L, while fluctuating between 1.06% and 18.58%. A total of 134 samples collected between 2015 and 2017 at Anonymous Hospital in Bangkok, Thailand, showed reduced sensitivity to ceftriaxone in two samples, both of which had similarities to those from the United Kingdom, the United States and the Netherlands.²² Also, we identified an isolate of ceftriaxone-resistant *N. gonorrhoeae* in China, the strain genotype is the same as the resistant clone FC428 that originated in Japan.^{23,24} In comparison to the ceftriaxone drug susceptibility studies in domestic and foreign countries, the CDC statistics reveals that the percentage of reduced ceftriaxone susceptibility (MIC \geq 0.125 mg/L) in 5865 clinical gonococci strains collected domestic from 2000 to 2010 increased from 0.10% in 2000 to 0.30% in 2010.²⁵ Meanwhile, surveillance data from Fukuoka, Japan, showed that gonococcal strains with low ceftriaxone susceptibility in the region increased from 2.50% in 2000 to 4.00% in 2012 ($p>0.05$).²⁶ The Chinese gonococcal drug resistance surveillance system showed that among 3849 gonococcal clinical strains collected in seven provinces in China from 2013 to 2016, ceftriaxone hypersensitive strains fluctuated between 9.70% and 12.20%, with a total hypersensitivity rate of 10.80%.²⁷ Aligning with the overall ceftriaxone hypersensitivity rate in China, the trend of resistance to ceftriaxone in Zhejiang would still require further monitoring of gonococcal over time. Due to the increasing international spread of ceftriaxone-resistant strains, there is a need to strengthen international cooperation to monitor and trace the spread of ceftriaxone-resistant clones.^{28,29}

Spectinomycin, an amino cyclohexanol antibiotic found in *Streptomyces*, demonstrates strong antibacterial effect on *N. gonorrhoeae*. In our study, among 1710 clinical strains of *N. gonorrhoeae* collected in Zhejiang province from 2007 to 2021, only 3 and 1 spectinomycin-resistant strains were found in 2018 and 2019, respectively. Although the vast majority of clinical isolates were susceptible to spectinomycin, the alarming issue is that the ratio of strains with MIC ≥ 32 mg/L has been increasing from 2013 to 2021, with the MIC of resistant strains from 2018 reaches ≥ 256 mg/L. Considering that *N. gonorrhoeae* developed resistance soon after the previous antimicrobial drugs were put into use, an increasing gonococcal antibacterial tendency has been observed over the past 80 years. In particular, the increasing trend in the ratio of strains with MIC ≥ 32 mg/L surely worth a notice.

Azithromycin is a semisynthetic macrolide antibiotic that was used early as a treatment for bacterially transmitted infections, including gonorrhea. Like penicillin, tetracycline, and quinolone drug medications, azithromycin was generally highly sensitive to clinical strains when it was first applied in the treatment of gonorrhea. Simultaneously, case reports of gonococcal resistance soon began to appear worldwide.^{30,31} From a total of 5808 consecutive strains of *N. gonorrhoeae* were collected for antibiotic MICs evaluation in Guangdong region during 2013–2020, strains with resistance to azithromycin were observed to fluctuate between 8.60% and 20.03%.³² Between 2014 and 2020, 488 symptomatic gonococcal samples were received from 10 Thai military hospitals, and three samples were determined to be insensitive to azithromycin.³³ In this study, surveillance of gonococcal azithromycin resistance in Zhejiang from 2013 to 2021 showed that the azithromycin-resistant *N. gonorrhoeae* fluctuated between 12.0% and 36.2% among 1157 clinical strains. Overall, the ratio of azithromycin-resistant strains rises over time, with the ratio of azithromycin strains at 12.0% in 2013 increased to 22.0% in 2014, in 2015 reached 36.2%. Correspondently, the MIC₅₀ of clinical strains of azithromycin isolated in Zhejiang also increased from 0.125 mg/L in 2013 to 0.5 mg/L in 2018. Consequently, monotherapy with azithromycin is no longer recommended.

Conclusion

According to WHO guidelines for the treatment of gonorrhea, an antibiotic should not be considered as the drug of choice in a given region when resistance surveillance data indicate antibiotic resistance rates $>5\%$. Therefore, for Zhejiang, ciprofloxacin, penicillin and azithromycin resistance rates have exceeded 5%, they should not be recommended for *N. gonorrhoeae* treatment. Spectinomycin and ceftriaxone are more sensitive and still suitable for clinical treatment. At the same time, it is necessary to continuously monitor the drug susceptibility of *N. gonorrhoeae* in the region to understand the drug resistance trend in time, to provide a basis for clinical treatment and precise treatment of *N. gonorrhoeae* patients in the region, in order to curb the drug resistance trend of *N. gonorrhoeae* and the emergence of highly resistant strains.

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The ethics of this study (approval number 2011-KY-003) was approved by the Medical Ethics Committee at the Institute of Dermatology, the Chinese Academy of Medical Sciences & Peking Union Medical College and the National Center for Sexually Transmitted Disease Control at Nanjing. Written informed consent was obtained from all participants or the caretakers of the minors/children in the study. Study participants signed an informed consent form before inclusion in the study. The study complies with the Declaration of Helsinki.

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Disclosure

The authors declare no conflicts of interest in this work.

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