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**Original Article**

# Surveillance of the Antimicrobial Susceptibility of *Neisseria gonorrhoeae* Isolates Collected in Changsha, China from 2003 to 2015

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**SUMMARY:** A total of 1,294 *Neisseria gonorrhoeae* isolates obtained in Changsha, China from 2003 to 2015 were examined for their susceptibility to penicillin (PEN), ciprofloxacin (CIP), spectinomycin (SPT), and ceftriaxone (CRO) using the disc diffusion method. In addition, the minimum inhibitory concentrations (MICs) of CRO for 460 isolates collected during 2008–2015 was determined by agar dilution method. Isolates with intermediate CRO susceptibility were additionally tested for azithromycin susceptibility. Results demonstrated that the rate of resistance to PEN and CIP were 77.5 % and 94.2 %, respectively. Only 4 SPT-resistant and 2 SPT-intermediate isolates were identified. No CRO-resistant isolates were identified, although the percentage with intermediate susceptibility increased from 1.8% in 2012 to 11.9% in 2015. Among these, 3 isolates showed no susceptibility to azithromycin with 2 isolates showing an MIC of 0.5 μg/mL and 1 isolate showing an MIC of 1.0 μg/mL. We recommend azithromycin for treating strains that demonstrate intermediate susceptible to CRO and azithromycin-susceptible *N. gonorrhoeae* isolates occurring in Changsha.

## INTRODUCTION

*Neisseria gonorrhoeae* is the etiological agent of the sexually transmitted disease (STD) gonorrhea. In 2008, the World Health Organization (WHO) estimated there were more than 106.1 million new cases of gonorrhea among adults worldwide (1). In China, 95,263 cases of gonorrhea were reported, and gonorrhea is ranked as the sixth most common infectious disease in 2012 (2). Gonorrhea can cause serious complications such as epididymitis, ectopic pregnancy, and infertility, while also predisposing carriers to the acquisition of human immunodeficiency virus infection (3). Currently, no vaccine for gonorrhea is available, so effective antimicrobial agents are the main treatment for this infectious disease.

However, the antimicrobial resistance (AMR) developed by *N. gonorrhoeae* is posing a challenge to the management of this infection worldwide. During the past 3 decades, *N. gonorrhoeae* isolates have developed resistance to penicillin (PEN), tetracycline, and ciprofloxacin (CIP) (4,5). In addition, *N. gonorrhoeae* are also gradually developing decreased susceptibility to extended-spectrum cephalosporins (ESCs), which are the only remaining options for empirical first-line treatment (6,7). Treatment failures due to the development of antibiotic resistance have been reported in Japan (8), Australia (9), and South Africa (10). Moreover, in 2011 and 2012, the first extensively drug-resistant *N. gonorrhoeae* strains that showed high-level resistance to cephalosporins, the "super bugs" (H041 and F89), were identified in Japan (11) and France (12). To address the spread of resistant isolates, the Centers for Disease Control and Prevention (CDC) of the United States issued a public response plan in 2012 to improve surveillance and mitigate the impact of *N. gonorrhoeae* resistance to ceftriaxone (CRO) and cefixime (13). Systematic surveillance of *N. gonorrhoeae* AMR at the local, regional, national, and global level helps detect the emergence of new resistant strains, monitor the changing patterns of susceptibility, and enable timely updates to recommended treatment strategies.

Since 1992, China has been part of the WHO Western Pacific Region (WPR) Resistance Surveillance Program; however, for several years, the reported data were only limited to several cities, such as Guangzhou (14), Nanjing (15), and Shanghai (16), and the AMR profiles were basically consistent with the patterns found in other regions of the WPR. To our knowledge, there has been no monitoring the AMR of *N. gonorrhoeae* in Changsha, a megacity close to Guangzhou, where STD incidence is one of the highest in China. This study aimed to analyze the changing antimicrobial resistance profile of *N. gonorrhoeae* isolates collected in Changsha, China over the period of 2003–2015 to PEN, CIP, spectinomycin (SPT), and CRO, using the disk diffusion (K-B) method. The CRO minimum inhibitory concentrations (MICs) during 2008–2015 were also determined by agar dilution method.

## MATERIALS AND METHODS

***N. gonorrhoeae* isolation and verification:** A total of 1,249 *N. gonorrhoeae* isolates were consecutively collected from patients attending STD clinics in 4 general hospitals in Changsha, China from 2003 to 2015. The number of gonorrhea cases included in this study accounted for approximately 18%–20% of the total re-

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ported cases from the city. Of the patients, 94.2% were from men (median age, 36.2 years), and 5.8% were from women (median age, 33.2 years). The sites of isolation were as follows: urogenital, 91.5%; endocervical swabs, 4.9%; throat, 0.8%; and not reported, 2.8%. The specimens were directly inoculated onto Thayer-Martin medium and cultured in an atmosphere of 5% $CO_2$ at 37°C for 24–48 h. All isolates were identified on the basis of gram-stained smears, colony morphology, oxidation reaction, and sugar fermentation. Isolates collected during 2008–2015 were stored at −70°C until use.

**Antimicrobial susceptibility testing:** Isolates were examined for susceptibility to PEN (10 U), CIP (5 μg), SPT (100 μg), and CRO (30 μg), using the K-B method, as per the Clinical and Laboratory Standards Institute (CLSI) guidelines (17). Since there were no criteria for intermediate susceptibility or resistance to CRO in the CLSI guidelines, isolates were assigned only as susceptible or non-susceptible (NS). In addition, the MIC for CRO was determined by the agar dilution method for 460 *N. gonorrhoeae* isolates collected in 2008–2015, according to the CLSI Document M7-A8 (M100-S21) (18). For isolates with intermediate susceptibility to CRO, we additionally determined the MICs of azithromycin. The MICs for CRO were assessed over a range of 0.002–1.0 μg/mL, and the sensitivity of each isolate was determined according to the WHO WPR Resistance Surveillance Programme. Isolates with an MIC ≥ 1.0 μg/mL were classified as resistant, those with 0.125 ≤ MIC ≤ 0.50 μg/mL as intermediate, and those with an MIC ≤ 0.06 μg/mL as sensitive.

MICs for azithromycin were assessed over a range of 0.002–4.0 μg/mL. Isolates with an MIC ≥ 2.0 μg/mL were classified as resistant, those with 0.5 ≤ MICs ≤ 1.0 μg/mL as intermediate, and those with an MIC ≤ 0.25 μg/mL as sensitive. *N. gonorrhoeae* strain ATCC 49226 was used as a control for disc diffusion and MIC testing.

**Statistical analysis:** Differences in the rates of the *N. gonorrhoeae* antimicrobial resistance were statistically compared by the Chi-square test and *p*-values were determined using SPSS ver. 19.0 (Chicago, IL, USA).

## RESULTS

**Antimicrobial resistance to PEN, CIP, SPT, and CRO, as assessed by the K-B method on *N. gonorrhoeae* strains collected from 2003 to 2015:** Of the 1,249 *N. gonorrhoeae* isolates obtained from 2003 to 2015, 968 were PEN-resistant. The prevalence of PEN resistance percentage was constant between the periods of 2003–2005 and 2006–2008 but markedly declined from 84.6% in 2006–2008 to 68.3% in 2009–2011 ($\chi^2$ = 12.953, $p < 0.001$) and then held steady at 63.9% until 2012–2015. The total rate of CIP resistance was 94.2 %. The resistance rate decreased from 95.6% in 2003–2005 to 88.6% in 2006–2008 before increasing to 89.4% in 2009–2011 and finally 94.2% in 2012–2015. Of the 4 antibiotics tested, CRO and SPT appeared to be the most effective agents. All isolates were susceptible to SPT with the exception of 4 that were resistant and 2 with intermediate susceptibility. The MICs for the 6 non-susceptible isolates were confirmed by the agar dilution method. The proportions of CRO non-susceptible ($CRO^{ns}$) and $CRO^{ns}$-associated PEN- and CIP-resistant (PEN-CIP-$CRO^{ns}$) isolates were less than 5% from 2003–2011 but increased to 9.1% ($\chi^2$ = 6.831, $p$ = 0.009) and 7.2% ($\chi^2$ = 10.468, $p$ = 0.001) in 2012–2015, respectively (Table 1).

Table 1. Susceptibility profiles of *N. gonorrhoeae* to penicillin, ciprofloxacin, spectinomycin, and ceftriaxone by the K-B method from 2003 to 2015

| Year | 2003–2005 | 2006–2008 | 2009–2011 | 2012–2015 | Total |
|---|---|---|---|---|---|
| Penicillin (PEN) | | | | | |
| S | 14 (2.1) | 2 (1.1) | 3 (1.7) | 4 (1.9) | 23 (1.8) |
| I | 108 (15.7) | 25 (14.3) | 54 (30.0) | 71 (34.1) | 258 (20.7) |
| R | 564 (82.2) | 148 (84.6) | 123 (68.3)[1)] | 133 (63.9)[1)] | 968 (77.5) |
| Ciprofloxacin (CIP) | | | | | |
| S | 23 (3.8) | 1 (0.6) | 0 | 0 | 24 (2.0) |
| I | 4 (0.6) | 9 (10.8) | 19 (10.6) | 12 (5.8) | 44 (3.8) |
| R | 590 (95.6) | 156 (88.6) | 161 (89.4) | 196 (94.2) | 1,103 (94.2) |
| Spectinomycin (SPT) | | | | | |
| S | 676 (99.5) | 152 (99.4) | 179 (99.4) | 208 (100) | 1,215 (99.4) |
| I | 1 (0.1) | 0 | 1 (0.6) | 0 | 2 (0.2) |
| R | 3 (0.4) | 1 (0.6) | 0 | 0 | 4 (0.4) |
| Ceftriaxone (CRO) | | | | | |
| S | 641 (96.7) | 115 (98.3) | 172 (95.6) | 189 (90.9) | 1,117 (95.6) |
| NS | 22 (3.3) | 2 (1.7) | 8 (4.4) | 19 (9.1)[2)] | 51 (4.4) |
| PEN-CIP-$CRO^{ns}$ | 14 (2.0) | 1 (0.6) | 3 (1.7) | 15 (7.2)[3)] | 33 (2.8) |
| Total | 686 | 175 | 180 | 208 | 1,249 |

Results are No. (%). S, susceptible; I, intermediate; R, resistant; NS, non-susceptible.
PEN-CIP-$CRO^{ns}$, $CRO^{ns}$-associated penicillin- and ciprofloxacin-resistant.
[1)]: compared to 2006–2008 (2009–2011: $\chi^2$ = 12.953, $p < 0.001$; 2012–2015: $\chi^2$ = 20.699, $p < 0.001$).
[2)]: compared to 2006–2008 ($\chi^2$ = 6.831, $p$ = 0.009).
[3)]: compared to 2006–2008 ($\chi^2$ = 10.468, $p$ = 0.001).

Table 2. Ceftriaxone (CRO) susceptibility and MICs of *N. gonorrhoeae* isolates in Changsha from 2008 to 2015[1)]

| Year | No. of strains | Susceptibility | | | MICs (μg/mL) | | |
|---|---|---|---|---|---|---|---|
| | | S | I | R | $MIC_{50}$ | $MIC_{90}$ | MIC range |
| 2008 | 72 | 72 (100) | 0 | 0 | 0.015 | 0.03 | 0.002–0.06 |
| 2009 | 64 | 64 (100) | 0 | 0 | 0.03 | 0.06 | 0.004–0.06 |
| 2010 | 56 | 55 (98.2) | 1 (1.8) | 0 | 0.03 | 0.06 | 0.004–0.125 |
| 2011 | 60 | 57 (95.0) | 3 (5.0) | 0 | 0.015 | 0.06 | 0.004–0.25 |
| 2012 | 62 | 56 (90.3) | 6 (9.7) | 0 | 0.03 | 0.06 | 0.004–0.25 |
| 2013 | 54 | 46 (85.2) | 8 (14.8) | 0 | 0.03 | 0.125 | 0.004–0.50 |
| 2014 | 50 | 46 (92.0) | 4 (8.0) | 0 | 0.03 | 0.06 | 0.004–0.25 |
| 2015 | 42 | 37 (88.1) | 5 (11.9) | 0 | 0.06 | 0.125 | 0.008–0.50 |
| Total | 460 | 433 (94.1) | 27 (5.9) | 0 | 0.03 | 0.06 | 0.002–0.50 |

[1)]: According to the WHO WPR Resistance Surveillance Programme.
CRO MIC ≥ 1.0 μg/mL were classified as resistant (R);
0.125 ≤ MICs ≤ 0.5 μg/mL as intermediate susceptible (I); MIC ≤ 0.06 μg/mL as sensitive (S).

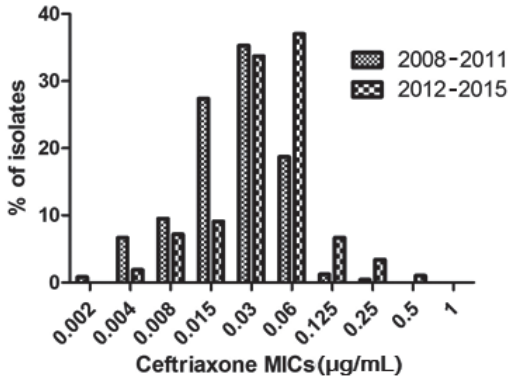


Fig 1. Distribution of ceftriaxone (CRO) MICs of *N. gonorrhoeae* isolates in Changsha during the period of 2008–2011 and 2012–2015.

**CRO susceptibility status and MIC for *N. gonorrhoeae* strains collected in Changsha from 2008 to 2015:** The CRO susceptibility status and MIC were determined for 460 strains collected from 2008 to 2015 and are shown in Table 2. No resistant strains were found during the 8-year period, while a total of 27 (5.9%) isolates with intermediate susceptibility were identified. The percentage of isolates with intermediate susceptibility increased from 0% in 2008 to 11.9% in 2015, with a peak of 14.8% in 2013. The highest MIC determined was 0.5 μg/mL, which accounted for 0.4% of the isolates tested (2/460). The $MIC_{50}$ and $MIC_{90}$ rose from 0.015 μg/mL and 0.03 μg/mL in 2008 to 0.06 μg/mL and 0.125 μg/mL in 2015, respectively. The MIC distribution for CRO in 2008–2011, compared with that for in 2012–2015, showed a decreased proportion of highly susceptible gonococcal isolates (MIC ≤ 0.03 μg/mL) (Fig. 1). Furthermore, among the 27 isolates of intermediate CRO susceptibility, 3 were non-susceptible to azithromycin, 2 and 1 of these exhibited MICs of 0.5 and 1 μg/mL, respectively.

## DISCUSSION

In this study, we observed that the percentage of PEN-resistant *N. gonorrhoeae* strains in Changsha, China decreased remarkably from 84.6% in the period of 2006–2008 to 63.9% during 2012–2015. We speculate that a reduction in the use of PEN in recent years in Changsha may have contributed to this decrease. More than 88% of the status analyzed demonstrated resistance to CIP. This is higher than the prevalence reported those in a previous study reported by Zou et al. (19) in Changsha (77.91% in 2000), indicating an increased resistance in this region during the last decade. However, the rate reported in our study is slightly lower than that reported from other parts of China, such as Nanjing (15) (98.99% in 2006) and Guangzhou (14) (98.0% in 2008–2013). Similar results were also reported in Southeast Asia (20). In addition, no isolate susceptible to CIP has been found since 2008. Due to the high rate of resistance worldwide, PEN and CIP have not been recommended for the treatment of gonorrhea.

In contrast to PEN and CIP, non-susceptibility to SPT in our findings was rare, with only 4 resistant and 2 intermediate strains detected over 13 years. These results were also consistent with reports by the WHO in the WPR, where excellent sensitivity to SPT was described. However, the prescription of SPT has been limited for a number of reasons. Firstly, it is only effective for urethral and rectal infections but not for pharyngeal infections, which are asymptomatic but increasingly common, particularly in men who have sex with men (21). Secondly, a novel mechanism for the generation of high level of SPT resistance was recently reported in a Norwegian strain because of mutations in the gonococcal gene encoding ribosomal protein S5 (22). Third-generation cephalosporins are the recommended antibiotics for the treatment of gonorrhea, and the popularity of these drugs has been maintained in guidelines and the clinical practice of gonorrhea treatment. However, it is concerning that susceptibility to CRO (injectable) and cefixime (oral) has decreased globally in recent years. In our surveillance of 1,249 isolates collected during the period of 2003–2015 and assessed by the K-B method, the percentage of $CRO^{ns}$ isolates increased from 1.7% in 2006–2008 to 9.1% in 2012–2015. Addition to the K-B method used for clinical use, we re-tested theses isolates to identify their CRO MIC by way of the agar dilution method because the *N. gonorrhoeae* isolates collected from 2008 to 2015 were still available. The results showed that the rate of intermediate susceptibility, as well as its MIC range, $MIC_{50}$, and $MIC_{90}$ significantly increased, which was consistent with the findings in Shanghai (11.9% in 2004–2005). Furthermore, the proportion of highly susceptible gonococcal isolates

during 2008–2011 was lower than that in the period of 2012–2015. Elevated MICs were also reported in other countries. In Canada between 2000 and 2009 ($n$ = 40,875), the CRO modal MIC had shifted from 0.016 μg/mL in 2000 to 0.063 μg/mL in 2009 (23). In British Columbia (2006–2011), 12% of isolates (227/1,837) showed a CRO MIC of 0.064 μg/mL, and 1% of isolates (27/1,837) showed a MIC of 0.125 μg/mL (24).

As most gonorrhea patients also have *Chlamydia trachomatis* infections, the CDC in the United States recommends combination therapy of CRO and azithromycin for complex gonorrhea treatment. Our results showed that 3 strains had both intermediate susceptibility to CRO and non-susceptibility to azithromycin. These strains will be a tricky to treat. New drugs should be investigated for gonorrhea treatment in the future. In light of our findings, we recommend azithromycin for treating *N. gonorrhoeae* isolates occurring in Changsha that have intermediate susceptibility to CRO and are azithromycin susceptible.

Limited information is available regarding the multidrug resistance (MDR) trends of *N. gonorrhoeae* in China. However, considering the high frequency of resistance to PEN and CIP for gonococcal isolates, $CRO^{ns}$-associated MDR in China should not be overlooked. More than 5% of isolates were found to be $CRO^{ns}$-associated PEN- and CIP-resistant in Changsha during 2012–2015. Moreover, one isolate from a 40-year-old male patient in 2003 showed resistance to all 4 antibiotics. Unfortunately, the isolate was not adequately analyzed by the agar dilution method. The MDR of *N. gonorrhoeae* is associated with mutations in the gene at the specific chromosome locus; such broad resistance may be attributed to patient self-medication or non-standardized drug doses.

In summary, the antimicrobial resistance of *N. gonorrhoeae* to PEN and CIP is highly prevalent in Changsha, and there was a trend towards reduced sensitivity to CRO. Our findings highlight the importance of both regional and national surveillance programs and a prompt modification of treatment guidelines, which should reflect the changing patterns of gonococcal antimicrobial susceptibility in a timely manner.

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**Conflict of interest** None to declare.

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