

# Gentamicin susceptibility of *Neisseria gonorrhoeae* isolates from 7 provinces in China

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**Purpose:** Gentamicin is a promising antimicrobial for the treatment of gonorrhea. The study aimed to evaluate gentamicin minimum inhibitory concentrations (MICs) of *Neisseria gonorrhoeae* isolates in China.

**Methods:** In this study, the agar dilution method was used to determine the MICs of 470 isolates collected in 2016 to four effective antimicrobials (gentamicin, azithromycin, ceftriaxone, and spectinomycin).

**Results:** Gentamicin MICs ranged from 1 to 8 mg/L. No isolate was resistant to gentamicin. Of seven isolates simultaneously resistant to azithromycin and ceftriaxone, 6 isolates demonstrated MICs of 4 mg/L or less to gentamicin. No cross relationships were found between MICs of gentamicin and susceptibility profiles of azithromycin, ceftriaxone, and spectinomycin.

**Conclusion:** The in vitro results suggest that gentamicin can be a promising treatment option for gonococcal infections in China. Clinical trials to evaluate the therapeutic efficacy of gentamicin are required.

**Keywords:** *Neisseria gonorrhoeae*, agar dilution method, gentamicin, antimicrobial surveillance

## Introduction

*Neisseria gonorrhoeae* (*N. gonorrhoeae*) is a sexually transmitted pathogen causing gonorrhea, which is the fourth most commonly reported notifiable communicable disease in China, with 133,156 reported cases in 2018.<sup>1</sup> If left untreated, *N. gonorrhoeae* can cause adverse health outcomes. It also facilitates the transmission of HIV, causing immense morbidity and socioeconomic consequences.<sup>2</sup> Without an effective vaccine against *N. gonorrhoeae*, antimicrobials are the only medical approaches to gonococcal treatment and control. However, *N. gonorrhoeae* has developed resistance to multiple classes of antibiotics over the past 60 years, and previously effective therapeutics such as penicillin, tetracycline, and fluoroquinolones are no longer recommended.<sup>3</sup>

Ceftriaxone is currently recommended as the first-line treatment option for gonococcal infection in American, Australian, Canadian, Chinese, European, and World Health Organization (WHO) guidelines for the treatment of sexually transmitted diseases.<sup>4,5</sup> Azithromycin has also been prescribed as a part of dual treatment regimen. Besides, spectinomycin remains susceptible to a large amount of *N. gonorrhoeae* isolates and is used as an alternative treatment option.<sup>6,7</sup> Moreover, the emergence of *N. gonorrhoeae* isolates with a multidrug resistant or extremely-drug resistant profile highlights the importance of considering alternatives for future

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therapeutic options. Notably, in China, the rates of isolates resistant to azithromycin or with decreased susceptibility to ceftriaxone were high from 2013 to 2016, with 18.6% to azithromycin and 10.8% to ceftriaxone.<sup>8</sup> Although isolates resistant to spectinomycin were sporadic in China, its inferior efficacy for treating oropharyngeal infections and its high potential to develop resistance limits its application.<sup>6,9</sup>

Gentamicin has been recommended as an alternate therapy to ceftriaxone in American, European, and WHO guidelines.<sup>7,10,11</sup> In addition, it is an aminoglycoside antimicrobial that has been used in many developing countries to treat gonorrhea, with the advantage of having both high therapeutic efficacy and low cost.<sup>12</sup> However, there is no published data on gentamicin use in China. If gentamicin can be considered as part of an alternative strategy, the knowledge of the susceptibility of Chinese *N. gonorrhoeae* isolates to gentamicin is essential. This study evaluated gonococcal susceptibility to gentamicin in China for the first time, in conjunction with susceptibility testing for azithromycin, ceftriaxone, and spectinomycin. This study design allowed for the analysis of statistical relations between these four antimicrobials.

## Materials and methods

### Ethics approval

The ethics approval for the study was obtained from 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 (2014-LS-026) for the use of anonymized samples collected from patients attending local dermatology and/or Sexually Transmitted Disease clinics.

### Gonococcal isolates

Clinical isolates were consecutively collected from different clinics in 7 provinces (Beijing, Hainan, Liaoning, Sichuan, Tianjin, Xinjiang, and Zhejiang) within the China Gonococcal Resistance Surveillance Programme (China-GRSP) in from 1<sup>st</sup> January to 31<sup>st</sup> December 2016 as previously described.<sup>8</sup> At every clinic, routine medical treatments were provided as regular. Patients with inflammatory secretions or positive risk factors for gonococcal infection were sampled to conduct isolates cultures. Then samples were inoculated into selective Thayer-Martin (TM) medium and cultured at 36–36.5 °C in a moist 5% CO<sub>2</sub>-enrichment

atmosphere for 24–48 hrs. With the culture-positive isolates, presumptive *N. gonorrhoeae* isolate was identified based on colonial morphology (growth of typical appearing colonies), Gram stain (Gram-negative) and oxidase test (oxidase-positive diplococci in stained smears). If the identification of isolates were still ambiguous, sugar fermentation tests were further conducted. Subsequently, isolates were sub-cultured from the selective TM medium to a non-inhibitory medium. If the sub-cultured isolates were not pure, serial sub-cultures of individual colonies must be performed until a pure culture was obtained. After 18–20 hrs incubation, colonies of confirmed gonococcal isolates from the pure culture were suspended heavily in skim milk and frozen to –70 °C until transported to our reference laboratory at the National Center for Sexually Transmitted Disease Control, Chinese Center for Disease Control and Prevention (Nanjing, China). Then the frozen isolates collected in 2016 were randomly selected for further antimicrobial susceptibility tests. Of note, strains in Hainan, Sichuan, Tianjin, Xinjiang, and Zhejiang have been determined for susceptibility profiles to ceftriaxone and azithromycin in our previous study.<sup>8</sup>

### Antimicrobial susceptibility tests by agar dilution

Antimicrobial susceptibility tests of all of the isolates to gentamicin, azithromycin, ceftriaxone, and spectinomycin were determined by the agar dilution procedure. Specifically, the isolates were cultured from frozen skimmed milk onto selective TM medium and sub-cultured on GC agar base medium (Oxide, Hampshire, England) supplemented with 10% defibrinated sheep blood (Bianzhen Biotechnology, Nanjing, China) and 1% Iso VitaleX Enrichment (BD Diagnostics, New Jersey, USA) at 36 °C in a moist 5% CO<sub>2</sub>-enrichment atmosphere for 18–20 hrs. We used morphology and oxidase tests for repetitive gonococcal confirmation before antimicrobial susceptibility tests. Then colonies were scraped to the sterile saline solution (Pengyao Pharmacy, Wuxi, China), and the bacterial suspensions of 10<sup>7</sup> CFU were prepared. The suspension was inoculated to antibiotic-containing medium (GC agar base medium supplemented with 1% Iso VitaleX Enrichment) on a 9-cm diameter plate by using a multipoint inoculator (10<sup>4</sup> CFU per point). The plates were cultured at 36 °C in a moist 5% CO<sub>2</sub>-enrichment atmosphere for 18–24 hrs, and the growth of *N. gonorrhoeae* in different concentrations of antibiotic was observed and recorded.<sup>13</sup> For the four antibiotics, their concentrations were 1, 2, 4, 8, 16, and 32 mg/L for

gentamicin;  $\leq 0.125$ , 0.25, 0.5, 1, 2, and  $\geq 4$  mg/L for azithromycin;  $\leq 0.008$ , 0.015, 0.03, 0.06, 0.125, 0.25, and  $\geq 0.5$  mg/L for ceftriaxone; and  $\leq 8$ , 16, 32, 64, and  $> 64$  mg/L for spectinomycin. The minimum inhibitory concentration (MIC) of isolates was defined as the lowest concentration of the antibiotic that inhibited growth. Interpretive criteria were in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST, Version 8.1) guidelines to categorize profiles of susceptibility or resistance. For azithromycin, we categorized MIC as susceptibility (MIC  $\leq 0.5$  mg/L) or resistance (MIC  $\geq 1.0$  mg/L). For ceftriaxone, we defined MIC as susceptibility (MIC  $\leq 0.125$  mg/L) or resistance (MIC  $\geq 0.25$  mg/L). For spectinomycin, we categorized MIC as susceptibility (MIC  $\leq 64$  mg/L) or resistance (MIC  $> 64$  mg/L).<sup>14</sup> There are no standardized criteria for gentamicin in EUCAST and Clinical and Laboratory Standards Institute (CLSI) methodologies thus far. Previous published interpretative criteria were used: MIC  $\leq 4$  mg/L, susceptible; MIC 8–16 mg/L, intermediately susceptible; MIC  $\geq 32$  mg/L, resistant.<sup>15</sup> For quality assurance, four WHO *N. gonorrhoeae* reference strains (J, K, L, and P) were used as controls.<sup>16</sup>

## Data analysis

In this study, we described the distribution of the randomly selected and successfully cultured *N. gonorrhoeae* isolates and their MICs to gentamicin, azithromycin, ceftriaxone, and spectinomycin. Also, the rates were calculated to show the susceptibility profiles for the four antibiotics. Bivariate analyses of their susceptibility profiles were conducted by chi-square statistics between every two antimicrobials. The relationships between gentamicin MIC values and susceptibility profiles of azithromycin, ceftriaxone, and spectinomycin were analyzed by Wilcoxon Signed-Rank Test. A  $p$ -value  $< 0.01$  was considered statistically significant. Statistical analyses were carried out using Excel (Microsoft, Washington, USA) and SPSS software (IBM, New York, USA).

## Results

### Distribution of *N. gonorrhoeae* isolates

A total of 470 clinical *N. gonorrhoeae* isolates were randomly selected to test for antimicrobial susceptibility in 2016 from 7 provinces (Beijing, Hainan, Liaoning, Sichuan, Tianjin, Xinjiang, and Zhejiang). The geographic locations of these provinces and specific amounts were shown in Figure 1. The particular numbers were 64, 67, 60, 57, 74, 87, and 61, respectively. Among them, 339 isolates from Hainan, Sichuan, Tianjin, Xinjiang, and

Zhejiang were previously reported for their susceptibility to ceftriaxone and azithromycin.<sup>8</sup>

## Antimicrobial susceptibility

MIC values obtained from the WHO *N. gonorrhoeae* reference strains were identical or within 1 MIC dilution of those previously reported in every batch of tests, and they were excluded from the data analysis.<sup>16</sup> All of the 470 clinical isolates were determined for their MIC values to four antimicrobials. Gentamicin MICs ranged from 1 to 8 mg/L, and MIC<sub>50</sub> and MIC<sub>90</sub> were 4 mg/L and 8 mg/L (Table 1). Of 470 isolates, 404 (86.0%) demonstrated full susceptibility to gentamicin, 66 (14.0%) strains showing intermediate susceptibility, and none demonstrated resistance. Three hundred and twenty-five (69.1%) isolates were located at the breakpoint for susceptibility interpretation (MIC=4 mg/L), with 66 (14.0%) demonstrating one dilution greater than the breakpoint. Seventy-three (15.5%) isolates were resistant to azithromycin; 7 of these isolates also demonstrated intermediate susceptibility to gentamicin (chi-square=1.4,  $p=0.23$ ). Of the 19 (4.0%) isolates demonstrating resistance to ceftriaxone, 6 were intermediately susceptible to gentamicin (chi-square=3.6,  $p=0.06$ ). One of the two isolates resistant to spectinomycin demonstrated intermediate susceptibility to gentamicin. Seven (1.5%) isolates were resistant to azithromycin and simultaneously resistant to ceftriaxone (chi-square=5.3,  $p=0.02$ ); 6 of these isolates demonstrated full susceptibility to gentamicin. The  $p$ -values of cross relationships between gentamicin MICs and susceptibility profiles of other antibiotics were 0.94 for azithromycin, 0.29 for ceftriaxone, and 0.18 for spectinomycin (Table 1).

## Discussion

Increased resistance of *N. gonorrhoeae* over the past several years has limited the options for effective treatment and added considerable public health concern worldwide. Since *N. gonorrhoeae* is sporadically resistant to the current first-line antimicrobial, ceftriaxone, and this drug can cause allergic reactions, new antimicrobial need to be considered as an alternate. Other substitute recommendations shown decreased susceptibility worldwide for cefixime and high potential to develop resistance for spectinomycin.<sup>7,10,11</sup> Gentamicin was an effective and inexpensive antimicrobial that has been used in many developing countries to treat gonorrhea for over 20 years, without reports about its trend of declining susceptibility.<sup>17</sup> Furthermore, gentamicin has been listed as a treatment option



**Figure 1** Geographic locations of the provinces where the *Neisseria gonorrhoeae* isolates were collected from. The number of isolates from each provinces is given in the parentheses.

**Abbreviation:** n, number.

when treatment failure occurs after a dual therapy of ceftriaxone and azithromycin in WHO guidelines or resistance to extended-spectrum cephalosporin is identified in European guidelines.<sup>10,11</sup> In addition, gentamicin was recommended by the American Centers for Disease Control and Prevention (CDC) as a regimen to substitute for ceftriaxone in case of allergy, intolerance, and adverse reactions.<sup>7</sup> However, clinical trials for gentamicin (combining with azithromycin) are scarce, one showing full microbiological cure rate in 213 patients,<sup>18</sup> and the other indicating inferior potency to ceftriaxone particularly in pharyngeal and rectal infections.<sup>19</sup> In China, gentamicin has been prescribed clinically for gram-negative bacillary infections but not for gonorrhea due to the absence of its susceptibility data.

Evaluation of susceptibility *in vitro* is crucial to provide a rational basis for formulating more effective therapies for gonorrhea in the future. To our knowledge, the present study is the first surveillance of susceptibility of *N. gonorrhoeae* to gentamicin in China. Previous studies have assessed the gentamicin susceptibility by agar dilution method or E-test method in other countries. The Gonococcal Isolate Surveillance Project (GISP) in

America reported the data of gentamicin susceptibility on 10,403 gonococcal isolates collected in 2015 and 2016. Among these isolates, 73% demonstrated MICs from 8 to 16 mg/L, and 27% were 4 mg/L.<sup>20</sup> The 2009 survey of European gonococcal population's susceptibility to gentamicin found that 95% isolates were within a narrow MIC range (4–8 mg/L), with 79% showing a MIC of 8 mg/L.<sup>21</sup> The antimicrobial susceptibility surveillance conducted in Malawi found that after 14 years of use, all the isolates collected in 2007 were fully susceptible to gentamicin (MIC  $\leq$  4 mg/L).<sup>17</sup> Our findings also demonstrated the full susceptibility to gentamicin but differed from previous researches in showing lower MICs. With 85.9% isolates fully susceptible to gentamicin, MICs detected by agar dilution method in China were approximately one dilution lower than that in Europe and America, but consistent with their results from E-test method,<sup>15,21</sup> indicating that gentamicin may have treatment potency in China.

Our study showed that 15.3% gonococcal isolates were resistant to azithromycin, and 12.8% demonstrated decreased-susceptibility to ceftriaxone (according to the criteria in the previous study<sup>8</sup>). These results are consistent with our

**Table I** Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates in China

Antimicrobial	Profiles	Number of isolates for which MIC to Gen was				Total	p-value
		1 mg/L	2 mg/L	4 mg/L	8 mg/L		
Gentamicin		2	77	325	66	470	-
Azithromycin	Susceptible	2	65	271	59	397	0.94
	Resistant	0	12	54	7	73	
Ceftriaxone	Susceptible	2	73	316	60	451	0.29
	Resistant	0	4	9	6	19	
Spectinomycin	Susceptible	0	0	1	1	2	0.18
	Resistant	2	77	324	65	468	

**Abbreviation:** Gen, gentamicin.

surveillance data from 2013 to 2016 in China,<sup>8</sup> highlighting the importance of antimicrobial susceptibility surveillance and implications for future gonococcal treatment options. None of the isolates resistant to azithromycin or ceftriaxone were resistant to gentamicin, and we found no relationships between gentamicin MICs and susceptibility profiles of other antimicrobials, which is in tune with a previous study in India.<sup>22</sup> Relevant mutations in 23S rRNA, penicillin-binding protein 2 or efflux pump genes<sup>6</sup> causing the resistance of azithromycin or ceftriaxone may play no role in forming resistance in gentamicin. The in vitro results suggested that gentamicin might be an effective treatment option for the gonococcal patients who fail the dual therapy.

The present study is the first nationwide research reporting the *N. gonorrhoeae* susceptibility to domestically-produced gentamicin in China. Moreover, our results led to the preliminary foundation for the future implement of gentamicin for gonococcal infections in China. There are a few limitations to our study. Primarily, the antimicrobial susceptibility evaluation was conducted in vitro. The in vitro tests cannot analyze differences of the drug penetration in genital, rectal, or oropharyngeal sites. Also, a clinical trial of 720 participants indicated that gentamicin was inferior to ceftriaxone, particularly for pharyngeal and rectal infections. Furthermore, standardized resistance breakpoints for gentamicin have not been established by EUCAST and CLSI. The interpretative criteria used in our study was according to a previous study, which documented that MICs from treatment failure strains ranged from 4 to  $\geq 16$  mg/L.<sup>15</sup> Lastly, this study was a national survey of gentamicin susceptibility with isolates collected from 7 provinces in China, the strains account for only 0.4% (470/115,024) of reported cases of gonorrhea in 2016. Furthermore, the provinces located in central China have not been included

in our study (Figure 1). All of these potential biases may limit the generalizability of the current study to all the patients infected with gonorrhea in China.

## Conclusion

In conclusion, the current study was the first in vitro study on the susceptibility of *N. gonorrhoeae* to gentamicin with implications for a future treatment option for gonorrhea. Isolates with resistance to gentamicin were not observed in China as yet. The high incidence of gonorrhea coupled with increasing antimicrobial resistance to azithromycin and ceftriaxone warrants the consideration of alternative therapies. Gentamicin is an effective, inexpensive, and relatively safe antimicrobial that has been prescribed in Malawi,<sup>17</sup> whereas more clinical trials are needed for in vivo therapeutic efficacy. Our study for gentamicin assessment was included in the ROADMAP<sup>23</sup> (Resistance surveillance, Outcomes due to antimicrobial resistance, Antibiotic stewardship and application, Diagnostic tools, Mechanisms of antimicrobial resistance, Antimicrobial assessment, and Population pharmacokinetics and pharmacodynamics) plan. Moreover, it provided references to the future revision of the guidelines for the treatment of *N. gonorrhoeae* in China and gave hints of adding gentamicin as a routine surveillance antimicrobial in the China-GRSP. Furthermore, this project contributes to sibling countries for their gonococcal treatment, surveillance and control. Continued surveillance of gentamicin susceptibility and further investigation of gentamicin for clinical use are urgently needed.

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## Disclosure

The authors report no conflicts of interest in this work.

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