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Antimicrobial susceptibility of *Neisseria gonorrhoeae* isolates and syndromic treatment of men with urethral discharge in Kingston, Jamaica, 2018–19

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Objectives: To quantitatively determine the antimicrobial susceptibility of clinical *Neisseria gonorrhoeae* isolates from men with urethral discharge in Jamaica and to describe the syndromic treatment therapies administered.

Methods: Urethral eSwabs (Copan) were collected from 175 men presenting with urethral discharge to the Comprehensive Health Centre STI Clinic, Kingston, Jamaica. Clinical information was collected and MICs of eight antimicrobials were determined for *N. gonorrhoeae* isolates ($n = 96$) using Etest and interpreted using CLSI criteria.

Results: The median age of the subjects was 28 years (range: 18–73 years) with a median of 2 sexual partners (range: 1–25) per male in the previous 3 months. All examined *N. gonorrhoeae* isolates were susceptible to ceftriaxone (96/96), azithromycin (91/91), cefixime (91/91) and spectinomycin (91/91). For ciprofloxacin and gentamicin, respectively, 98.9% (91/92) and 91.3% (84/92) of the isolates were susceptible and 1.1% (1/92) and 8.7% (8/92) showed intermediate susceptibility/resistance. For tetracycline and benzylpenicillin, respectively, 38.0% (35/92) and 22.0% (20/91) of the isolates were susceptible, 52.2% (48/92) and 74.7% (68/91) showed intermediate susceptibility/resistance and 9.8% (9/92) and 3.3% (3/91) were resistant. Syndromic treatment was administered as follows: 93.1% received 250 mg of ceftriaxone intramuscularly plus 100 mg of doxycycline orally q12h for 1–2 weeks and 6.9% received 500 mg of ciprofloxacin orally plus 100 mg of doxycycline orally q12h for 1 week.

Conclusions: Ceftriaxone (250 mg) remains appropriate for gonorrhoea treatment in the examined population of men in Kingston, Jamaica. Surveillance of *N. gonorrhoeae* AMR should be expanded in Jamaica and other Caribbean countries to guide evidence-based treatment guidelines.

Introduction

Neisseria gonorrhoeae is estimated to cause approximately 87 million urogenital cases among adults worldwide each year.[1] Untreated or inappropriately treated infections can result in serious and sometimes permanent health problems[2] and persons with gonorrhoea have an increased risk of sexual acquisition and transmission of HIV.[3,4] Effective antibiotic treatment of gonococcal infections is crucial to avoid these sequelae, making appropriate treatment imperative to limit disease and also for preventing transmission to sexual partners.

The effectiveness of antimicrobial treatment has become increasingly limited due to *N. gonorrhoeae* antimicrobial resistance

(AMR) emerging to every antimicrobial that has been used as first-line treatment.[5] Local AMR data are recommended to support the choice of antimicrobial therapy[6] and national and international surveillance of AMR is essential globally.[7,8] However, exceedingly limited *N. gonorrhoeae* AMR data have been reported from the Caribbean, and from Jamaica the latest internationally published study examined gonococcal isolates from 1991 to 1996.[9] Furthermore, in that Jamaican study, the disc diffusion method, instead of a recommended method for MIC determination (agar dilution or MIC gradient strip tests), was used and only antimicrobials no longer recommended for first-line therapy for gonorrhoea were examined, i.e. benzylpenicillin and tetracycline.[9] In Jamaica, laboratory testing is highly limited and sexually transmitted infections (STIs) are treated syndromically per national guidelines.[10] Accordingly, AMR data for gonococcal strains currently circulating in Jamaica and in general in the Caribbean region are lacking. Our aims in this study were to quantitatively examine the susceptibility/resistance to eight therapeutic antimicrobials of *N. gonorrhoeae* isolates obtained from men with urethral discharge in Kingston, Jamaica, and to describe the syndromic antimicrobial treatment of these men.

Methods

Study design and sampling

This cross-sectional study included adult males with urethral discharge without antibiotic treatment (neither systemic nor topical) within 2 weeks prior to sampling. One hundred and seventy-five males >17 years of age presenting with urethral discharge to the Comprehensive Health Centre STI Clinic, Kingston, Jamaica, from 8 November 2018 to 21 June 2019 were enrolled consecutively, with the exception of the following time periods, during which there was insufficient clinic staffing: 17 to 26 November 2018; 15 December 2018 to 15 January 2019; and 4 to 13 June 2019. A single urethral swab (Copan eSwabs LQ Amies Minitip) was collected from each study participant. Patients are routinely managed syndromically (per national guidelines) without collection of genitourinary samples.[10]

Ethics

All participating males gave their informed consent before participating in this study. Ethical approval was obtained from the University of the West Indies Mona Campus Research Ethics Committee (ECP 222, 14/15), the Ministry of Health and the South East Regional Health Authority (2016/59).

Sample culture and *N. gonorrhoeae* identification

Swabs were stored at 4°C, transported with frozen ice packs to the laboratory, brought to room temperature and inoculated onto Thayer–Martin agar (BD, Diagnostics) supplemented with 1% BBL IsoVitaleX (BD, Diagnostics). After 48 h, suspected *N. gonorrhoeae* colonies were subcultured onto GC agar (BD, Diagnostics) supplemented with 1% BBL IsoVitaleX (BD, Diagnostics) for an additional 24 h. All cultures were incubated at 37°C in a humid 5% CO_2-enriched atmosphere. Isolated colonies with typical morphology that were rapid oxidase positive and Gram-negative diplococci on microscopy were presumptively identified as *N. gonorrhoeae*. All isolates presumptively identified as *N. gonorrhoeae* were stored at −80°C in tryptic soy broth prior to antimicrobial susceptibility testing.

Antimicrobial susceptibility testing

MICs of ceftriaxone, cefixime, azithromycin, ciprofloxacin, spectinomycin, benzylpenicillin, tetracycline and gentamicin were determined using Etest, in accordance with the manufacturer's instructions (bioMérieux). Antimicrobial susceptibility testing was performed on GC agar (BD, Diagnostics) supplemented with 1% BBL IsoVitaleX (BD, Diagnostics), which was incubated at 37°C in a humid 5% CO_2-enriched atmosphere for 24 h. The antimicrobial susceptibility testing was performed on batches of isolates (approximately six isolates per batch) and one of the 2016 WHO *N. gonorrhoeae* reference strains (K, G, O, P or L)[11] was included for quality control of each batch tested. Only whole MIC doubling dilutions were reported. The antimicrobial MICs (mg/L) for each isolate were classified as susceptible, intermediate and resistant, according to the current CLSI guidelines, where available. For ceftriaxone, cefixime and azithromycin, only susceptibility breakpoints are stated by the CLSI (www.clsi.org). For gentamicin, previously published susceptibility and resistance breakpoints were used.[12] According to CLSI guidelines (www.clsi.org), *N. gonorrhoeae* isolates susceptible to tetracycline were considered to also be susceptible to doxycycline. Finally, at the WHO Collaborating Centre for Gonorrhoea and Other STIs, Sweden, all isolates were verified as *N. gonorrhoeae* using MALDI-TOF MS (Microflex LT, Bruker Daltonik) and representative selected isolates (every fifth isolate) were retested using Etest. The essential agreement (±1 MIC log2 dilution) for each antimicrobial between the originally produced MICs and retesting MICs was >95%, indicating that the antimicrobial susceptibility testing performed in Jamaica was considered quality assured.

Statistical analysis

Pearson's χ^2 test (IBM SPSS Statistics® for Windows version 20) was used to determine associations between age and number of sexual partners each in the previous 3 months.

Results

Participating males and *N. gonorrhoeae* isolates

In total, 175 consenting males with urethral discharge were enrolled in the study. Of these 175 males, 96 (54.9%) were *N. gonorrhoeae* culture positive. The median age was 28 years (range: 18–73 years) for the 152 enrolled males providing information about both age and number of sexual partners. Men <50 years old represented 87.5% of participants and 38.2% of participants were <25 years old (Table S1, available as Supplementary data at *JAC* Online). The median number of self-reported sexual partners per male in the previous 3 months was 2 for the 152 participants who provided this information. The vast majority of participants (90.1%) had 1–5 sexual partners each in the previous 3 months, with 9.9% having ≥6 sexual partners in the previous 3 months (Table S1). Younger age was significantly associated with a greater number of sexual partners in the previous 3 months ($\chi^2 = 24.802$, $P = 0.016$).

Antimicrobial susceptibility/resistance

The MIC distributions of all eight examined antimicrobials are shown in Figure 1.

All viable *N. gonorrhoeae* isolates (100%) were susceptible to ceftriaxone (96/96), azithromycin (91/91), cefixime (91/91) and spectinomycin (91/91). For ciprofloxacin and gentamicin, respectively, 98.9% (91/92) and 91.3% (84/92) of the isolates were susceptible and 1.1% (1/92) and 8.7% (8/92) showed intermediate susceptibility/resistance. For tetracycline and benzylpenicillin, respectively, 38.0% (35/92) and 22.0% (20/91) of the isolates were susceptible, 52.2% (48/92) and 74.7% (68/91) showed

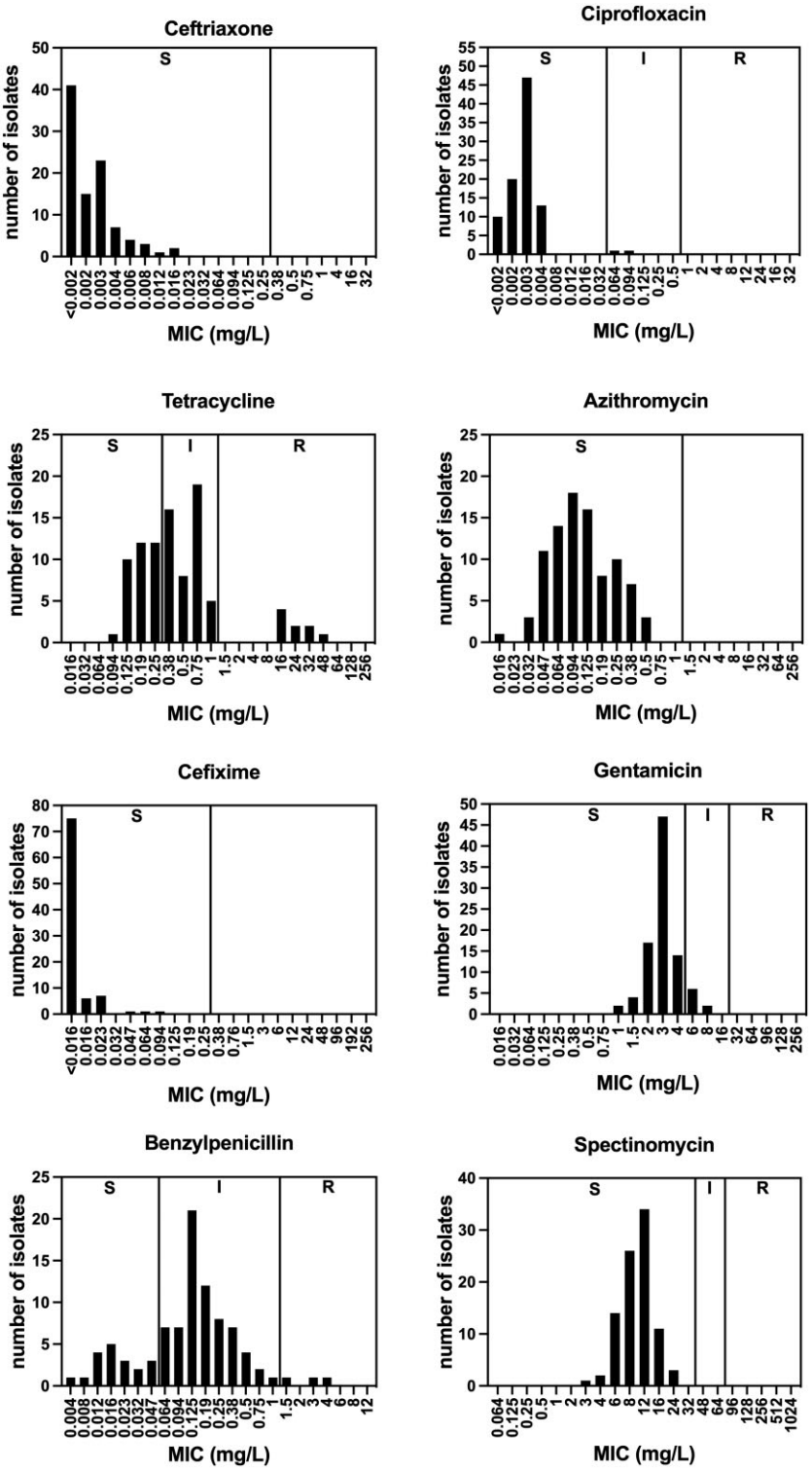

Figure 1. MIC distributions of eight therapeutic antimicrobials for *N. gonorrhoeae* isolates cultured in Kingston, Jamaica, 2018–19. Breakpoints in accordance with the current CLSI guidelines (www.clsi.org) are indicated. Previously published susceptibility and resistance breakpoints were used for gentamicin.[12] S, susceptible; I, intermediate; R, resistant. MIC_{50} values of the eight antimicrobials were as follows: ceftriaxone, 0.002 mg/L (range: <0.002–0.016 mg/L); cefixime, <0.016 mg/L (range: <0.016–0.094 mg/L); ciprofloxacin, 0.003 mg/L (range: <0.002–0.094 mg/L); azithromycin, 0.094 mg/L (range: 0.016–0.5 mg/L); tetracycline, 0.38 mg/L (range: 0.094–48 mg/L); gentamicin, 3 mg/L (range: 1–8 mg/L); benzylpenicillin, 0.125 mg/L (range: 0.004–4 mg/L); and spectinomycin, 12 mg/L (range: 3–24 mg/L).

Table 1. Syndromic urethral discharge therapies administered to males in Kingston, Jamaica, 2018–19

Therapy administered	*n*	%
Therapy 1 ceftriaxone 250 mg (intramuscularly STAT) AND doxycycline 100 mg (orally q12h for 1–2 weeks) AND metronidazole 500 mg (orally q12h for 1–2 weeks) OR metronidazole 2 g (orally STAT)	163	93.1
Therapy 2 ciprofloxacin 500 mg (orally STAT) AND doxycycline 100 mg (orally q12h for 1 week) AND metronidazole 500 mg (orally q12h for 1 week) OR metronidazole 2 g (orally STAT)	12	6.9

intermediate susceptibility/resistance and 9.8% (9/92) and 3.3% (3/91) were resistant.

Syndromic treatment of participants

Ceftriaxone and doxycycline were prescribed for 93.1% (163/175) of males and ciprofloxacin and doxycycline were prescribed for 6.9% (12/175) of males (Table 1). Metronidazole of various doses and durations were also included in the syndromic treatment. Accordingly, the males were treated syndromically, according to the national guidelines,[10] with all receiving gonorrhoea treatment with 250 mg of ceftriaxone [intramuscularly immediately (STAT)] or 500 mg of ciprofloxacin (orally STAT) plus chlamydia treatment with 100 mg of doxycycline orally q12h for 1–2 weeks (Table 1).

Discussion

In the present study, higher levels of *N. gonorrhoeae* resistance were observed for benzylpenicillin and tetracycline (including doxycycline), with extensive intermediate susceptibility/resistance to benzylpenicillin. These data are consistent with the high levels of penicillin- and tetracycline-resistant *N. gonorrhoeae* previously reported in the Caribbean.[9,13–16] The *N. gonorrhoeae* resistance to benzylpenicillin and tetracycline/doxycycline and extensive intermediate susceptibility/resistance to benzylpenicillin observed in this study are not surprising, as these antimicrobials have been extensively used for treatment for many decades. However, benzylpenicillin has not been recommended as a treatment option since the 1993 update of the national STI treatment guidelines.[17]

Few *N. gonorrhoeae* AMR surveillance studies have been performed in the Caribbean region in the last decade. The most recent study from Cuba did not identify any ceftriaxone-resistant *N. gonorrhoeae* isolates during 2010–11, though one isolate from 2010 had an MIC of 0.25 mg/L (the highest MIC value considered by the CLSI to be susceptible).[13] The ceftriaxone MIC_{50} for these 2010–11 *N. gonorrhoeae* Cuban isolates was 0.008–0.016 mg/L,[13] which is substantially higher than the ceftriaxone MIC_{50} for Jamaican isolates (0.002 mg/L) in our present study. In 2014, Puerto Rico reported one ceftriaxone-resistant *N. gonorrhoeae* isolate,[18] but, to the best of our knowledge, no other ceftriaxone-resistant *N. gonorrhoeae* isolates have been reported from the Caribbean. Due to the highly limited number of *N. gonorrhoeae* AMR surveillance studies, it is possible that additional ceftriaxone-resistant strains are spreading in the Caribbean. Surveillance of ciprofloxacin resistance in *N. gonorrhoeae* is even more limited in the Caribbean, with only decade-old data from Cuba.[13,19] Ciprofloxacin-resistant isolates were not identified in Cuba prior to 2009, but 71.4% of 2010 and 48.3% of 2011 isolates were resistant to ciprofloxacin.[13,19] Neither ciprofloxacin-resistant nor ceftriaxone-resistant *N. gonorrhoeae* isolates were identified in the present study, indicating the suitability of these antimicrobials for treatment of gonorrhoea in the population examined and in keeping with the most recent updated national guidelines that recommend 250 mg of ceftriaxone (intramuscularly STAT) as the preferred treatment option and 500 mg of ciprofloxacin (orally STAT) as an alternative treatment option.[10] However, expanded and regular AMR surveillance, including at a minimum ceftriaxone and ciprofloxacin, in Jamaica is imperative.

It is unclear why *N. gonorrhoeae* AMR appears limited among male gonorrhoea patients in Jamaica, particularly to ciprofloxacin and ceftriaxone that have been used as treatment options for approximately three decades,[10,16] though several possibilities exist. We did not collect information regarding sexual orientation, making it possible that all sexual orientation groups were not represented. Men who have sex with men have been described in several regions to be a group at increased risk for gonorrhoea and can also be more likely than men who have sex with women to have infections caused by AMR *N. gonorrhoeae*.[20,21] Another possible explanation for the low levels of *N. gonorrhoeae* resistance documented in the present study is that the population examined in Kingston may be more isolated from international tourism, which predominantly occurs on the north and west coasts of Jamaica. As *N. gonorrhoeae* AMR is commonly initially introduced from other countries,[22] it is possible that tourist-dense areas in Jamaica may have a different *N. gonorrhoeae* AMR profile.

In conclusion, the results of our study provide important information to limit the spread of *N. gonorrhoeae* AMR in the Caribbean region and inform Jamaican STI treatment guidelines. Ceftriaxone remains appropriate for gonorrhoea treatment in Jamaica. However, if the limited resistance to ciprofloxacin can be confirmed in the broader Jamaican population, usage of ciprofloxacin, instead of ceftriaxone, may be a more prudent current treatment choice for gonorrhoea in Jamaica, especially if expanded and regular AMR surveillance is implemented and also if molecular testing to confirm ciprofloxacin susceptibility is implemented to inform treatment. This could extend the useful life of ceftriaxone for treating gonorrhoea in Jamaica. Expanding *N. gonorrhoeae* AMR surveillance to additional populations in Jamaica, as well as to other Caribbean countries, should be a high priority.

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Transparency declarations

None to declare.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Clinical and Translational Science Institute or the National Institutes of Health.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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