Susceptibility of *Neisseria gonorrhoeae* against a dual treatment antibiotics regimen in primary health centres in Surabaya, Indonesia

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Background and objective
There were 82.4 million new gonorrhoea cases worldwide in 2020. Dual treatment with ceftriaxone or cefixime and azithromycin or doxycycline is currently recommended for gonorrhoea in Indonesia. However, reduced susceptibility and resistance to cephalosporins and azithromycin are increasing. We evaluated the susceptibility pattern of *Neisseria gonorrhoeae* to cefixime, ceftriaxone, azithromycin and doxycycline.

Methods
N. gonorrhoeae isolates were obtained from 19 male participants with clinically and laboratory-confirmed gonorrhoea. Antibiotic susceptibility testing was conducted by disc diffusion and interpreted according to Clinical and Laboratory Standards Institute and Centers for Disease Control and Prevention criteria.

Results
Reduced susceptibility or resistance was observed against doxycycline in 19 isolates (100%), cefixime in six (31.6%), ceftriaxone in three (15.8%) and azithromycin in zero (0%) isolates.

Discussion
A dual treatment regimen with ceftriaxone and azithromycin can still be recommended as first-line therapy for gonorrhoea in Indonesia. Antibiotic susceptibility surveillance of *N. gonorrhoeae* should be routinely conducted.

THE WORLD HEALTH ORGANIZATION (WHO) reported approximately 82.4 million new gonorrhoea cases in 2020, which did not change considerably from 87 million cases in 2018. Among the six WHO regions, the Western Pacific Region, including Australia, and the South East Asia Region, including Indonesia, ranked first and second in the number of new gonorrhoea cases in 2020, with 23.2 and 21.1 million cases, respectively.[1] Local data from the Dermatology and Venereology Department of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, also showed that gonorrhoea represented 4.1% of new sexually transmitted infection (STI) cases from 2013 to 2015.[2]

The management and control of gonorrhoea has been complicated by the emergence of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae*.[3,4] In the 1930s, sulphonamides were the first effective antibiotics for gonorrhoea, but resistance developed within the decade. In the 1940s, penicillin became the drug of choice for gonorrhoea. However, chromosomal-mediated resistance rapidly developed, resulting in a more than 100-fold increment in the penicillin dose required to cure gonorrhoea. In the 1970s, the emergence of penicillinase-producing *N. gonorrhoeae* (PPNG) rendered penicillin ineffective. Similarly, the introduction of tetracycline, spectinomycin and fluoroquinolones to treat gonorrhoea was followed by widespread resistance, leading to their discontinuation as drugs of choice.[5,6] In the 1990s, third generation cephalosporins, ceftriaxone and cefixime, were introduced for gonorrhoea. In 2010, due to the decreasing susceptibility of *N. gonorrhoeae* against these antimicrobials and frequent coinfection with chlamydia, a dual treatment regimen with an increased dose of cephalosporins and either doxycycline or azithromycin was recommended to curb the resistance to cephalosporins.[4–7] Nevertheless, the minimum inhibitory concentrations (MICs) of the constituents of this regimen gradually increased. In 2017–18, the WHO reported 0–21% gonococci isolates with reduced susceptibility (RS) to ceftriaxone, 0–22% with RS to cefixime and 0–60% with resistance to azithromycin worldwide.[3] In 2019, there were 97.1% gonococci isolates resistant to tetracycline but none with RS to ceftriaxone in Jakarta, Indonesia.[8] In 2021, the Australian Gonococcal Surveillance Program reported 0.9% gonococci isolates with RS, one isolate with resistance to ceftriaxone

and 4.7% isolates with resistance to azithromycin.[9] In the 2021 STI guidelines, the Centers for Disease Control and Prevention (CDC) recommend monotherapy with intramuscular injection of ceftriaxone as the first-line treatment for uncomplicated gonorrhoea.[4] However, a dual treatment regimen for gonorrhoea is still recommended in other countries such as Indonesia and Australia.[9,10]

The resistance of microorganisms against antimicrobials is typically defined by the in vitro MICs. However, for gonococci, elevated MICs do not always translate to in vivo treatment failure. For spectinomycin- or tetracycline-resistant *N. gonorrhoeae* or PPNG, very high MICs occurred with single-step mutation, which was responsible for clinical failure. However, for resistance to quinolone and extended-spectrum cephalosporins, a gradual increment in MICs occurred with stepwise accumulation of multiple genetic changes, resulting in a spectrum of gonococci with very low to very high MICs, before the emergence of isolates with complete resistance.[11] This gradual genetic alteration is mirrored in the current situation, where gonococci isolates with elevated MICs to cephalosporins are increasingly reported, but verified clinical failures are scarce.[12–14] This gradual process and increasing clinical and laboratory data have also led to changes in the interpretation of MICs overtime.[15,16] Currently, the term 'decreased susceptibility' is often used and denotes the MICs in which gonococcal isolates have been reported to cause treatment failures.[17]

Gonococcal AMR is a serious public health problem because it carries risks of treatment failure. Untreatable infection might lead to transmission to sexual partners and development of complications, including infertility, pelvic inflammatory disease, disseminated infection, neonatal infections after delivery and increased transmission of human immunodeficiency virus (HIV).[3,4] Thus, routine monitoring of the AMR pattern of *N. gonorrhoeae*, particularly against extended-spectrum cephalosporins and azithromycin, is crucial.[3] This study was conducted to evaluate the local AMR pattern of *N. gonorrhoeae* to dual treatment regimen constituents, namely ceftriaxone, cefixime, azithromycin and doxycycline, in primary health centres in Surabaya, Indonesia.

Materials and methods

Study design

This is a prospective study conducted across seven primary health centres in Surabaya, Indonesia: in Putat Jaya, Dupak, Perak Timur, Kedungdoro, Kedurus, Balong Sari and Sememi. The population of this study were male patients diagnosed with gonococcal urethritis based on clinical and laboratory findings. The inclusion criteria were male symptomatic patients with mucopurulent discharge on physical examination, presence of typical Gram-negative intracellular diplococci on Gram stain of the discharge, and growth of *N. gonorrhoeae* colonies in culture that were confirmed by oxidase, catalase and carbohydrate utilisation tests. The exclusion criteria were patients who were not willing to participate in the study. The sample size was calculated using the formula $N=[Z_{\alpha}^{2}\times p\times(1-p)]/d^{2}$, with α 0.05, Z_{α} 1.96, p (prevalence of *N. gonorrhoeae* isolates with RS or resistance to antibiotics) 0.05, d (precision) 0.1 and a result of 19. Participants were selected by consecutive sampling. The study was approved by the Surabaya Government Health Office (approval no. 072/16262/436.7.2/2017).

Data and specimen collection

Informed consent was obtained from each participant. The participants were asked questions about their age, sexual orientation, HIV status and previous medications. History-taking and inspection of urethral meatus were performed to identify mucopurulent discharge. The discharge was then sampled from navicular fossa using two sterile cotton swabs. The first swab was smeared on an object glass for Gram staining. The second swab was immediately applied to GC medium (Liofilchem, Roseto degli Abruzzi, Italy) supplemented with Vitalex growth supplement (Liofilchem, Roseto degli Abruzzi, Italy) and V.C.N.T Supplement (Liofilchem, Roseto degli Abruzzi, Italy) containing vancomycin, colistin, nystatin and trimethoprim for culture. Culture and antibiotic susceptibility testing were conducted at the Surabaya Health Laboratory Main Office, an accredited technical implementation unit of the Ministry of Health of the Republic of Indonesia.

Culture and identification of *N. gonorrhoeae*

The culture medium was immediately placed inside a tightly closed candle jar and incubated at 35–37°C. Growth of colonies was observed at 24 and 48 hours. *N. gonorrhoeae* had typical 0.5 mm, round colonies with transparent greyish white colour, a smooth and convex surface and a flat edge. Gram staining was performed on the colonies. If typical Gram-negative diplococci were found, identification tests were performed. *N. gonorrhoeae* isolates were confirmed with positive oxidase and catalase tests and a positive carbohydrate utilisation test only for glucose substrate.

Antibiotic susceptibility testing

Susceptibility testing to ceftriaxone, cefixime, azithromycin and doxycycline was carried out using the disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) criteria guidelines. Colony suspensions in 0.9% phosphate-buffered saline with a density of 0.5 McFarland units were prepared from confirmed *N. gonorrhoeae* colonies. The suspensions were recultured on GC Medium (Liofilchem, Roseto degli Abruzzi, Italy) supplemented with Vitalex Growth supplement (Liofilchem, Roseto degli Abruzzi, Italy). Antibiotic discs (Oxoid Limited, Hampshire, United Kingdom) containing ceftriaxone 30 µg, cefixime 5 µg, tetracycline 30 µg and azithromycin 15 µg were applied to the agar plates. The plates were incubated at 35–37°C in an anaerobic condition within a candle jar for 20–24 hours. The diameters of the inhibition zone were measured using a caliper from the bottom of the Petri dish. The diameters were then interpreted according to CLSI criteria for ceftriaxone (susceptible ≥35 mm, decreased susceptibility <35 mm), cefixime (susceptible ≥31 mm, decreased susceptibility <31 mm) and tetracycline/doxycycline (susceptible ≥38 mm, intermediate 31–37 mm, resistant ≤30 mm) and the CDC Neisseria Reference Laboratory for azithromycin (resistant ≤30 mm and not resistant >30 mm).[8,15,18] The mean inhibition zone diameters (IZDs) were also calculated. *N. gonorrhoeae* ATCC 49226 was used for quality control.

Results

Nineteen participants met the inclusion and exclusion criteria. Eleven participants were aged 17–25 years and eight participants were aged 26–36 years. Thirteen of the participants were heterosexual men and six were men who have sex with men (MSM). One MSM participant was HIV positive. Eleven participants had previously been treated by self-medication (nine participants) with ampicillin, tetracycline, amoxicillin, thiamphenicol and ofloxacin or by medical personnel (two participants) with cefixime and azithromycin regimen, while eight participants had received no previous treatment.

Table 1 shows the antibiotic susceptibility testing results for the *N. gonorrhoeae* isolates. Resistance or RS was most commonly observed against tetracycline/doxycycline in 19 isolates (100%), followed by cefixime in six isolates (31.6%) and ceftriaxone in three isolates (15.8%), with none (0%) against azithromycin. The mean inhibition zone diameters were 37.5 mm for ceftriaxone, 31.1 mm for cefixime, 34.2 mm for azithromycin and 21.2 mm for tetracycline/doxycycline.

Table 2 shows the antibiotic susceptibility testing results for the *N. gonorrhoeae* isolates grouped by sexual orientation of the participants. Compared to heterosexual participants, *N. gonorrhoeae* isolates from MSM participants had a higher percentage of RS against ceftriaxone (33.3% vs 7.7%) and cefixime (66.7% vs 15.4%). *N. gonorrhoeae* isolates from MSM participants also showed lower mean IZDs compared to heterosexual participants against cefixime (22.8 mm vs 34.9 mm), ceftriaxone (37.2 mm vs 37.6 mm) and azithromycin (32.5 mm vs 34.9 mm). One of the MSM participants with HIV infection had IZDs of 30 mm against ceftriaxone, 6 mm against cefixime, 33 mm against azithromycin and 25 mm against tetracycline/doxycycline.

Discussion

Our results reveal that 15.8% of gonococci isolates had RS to ceftriaxone. A rate of ≥5% RS to ceftriaxone was observed worldwide (0–21%), including in the Western Pacific Region (19.0% in Japan and 11.7% in China).[19] A study in Malang (Indonesia), a city within the same province as Surabaya, reported a similarly high rate (19.23%) of gonococci isolates with RS to ceftriaxone.[20] In contrast, a rate of <5% RS to ceftriaxone was reported in Vietnam (1.2%).[18,19] The Australian Gonococcal Surveillance Program reported a low rate (0.9%) of isolates with RS but one isolate resistant to ceftriaxone in 2021.[9] Other studies from Jakarta, Laos and Thailand observed no isolates with RS to ceftriaxone.[8,21,22] Our results show a lower mean IZD of ceftriaxone (37.5 mm) compared to that reported by Adamson et al for Vietnam (41.1 mm).[18]

In our study, 31.6% of gonococci isolates had RS to cefixime. A rate of ≥5% RS to cefixime was observed worldwide (0–22%) and in Malang (19.23%).[19,20] In contrast, a rate of <5% RS was reported in the Philippines (4.2%) and Vietnam (2.5%).[18,19] Other studies from Jakarta and Thailand observed no isolates with RS to cefixime.[8,22] Our results demonstrated a lower mean IZD of cefixime (31.1 mm) compared to that reported for Vietnam (36.3 mm).[18]

No gonococci isolates with resistance to azithromycin were observed in this study. A rate of <5% resistance to azithromycin was reported in Australia (4.7%) and Thailand (0.6%), while no resistance to azithromycin was reported for Bhutan.[9,19,22] In contrast, ≥5% resistance to azithromycin was observed in all six WHO regions: 26.1% in Vietnam, 26.0% in Japan and 6.8% in Singapore.[18,19] Our study showed a higher mean IZD of azithromycin (34.2 mm) compared to that reported for Vietnam (32.7 mm).[18]

Our study demonstrated that all gonococci isolates were resistant to tetracycline. A rate of ≥5% resistance to tetracycline was reported in Laos (99.4%), Jakarta (97.1%), Thailand (86.9%), Australia (41.0%) and Vietnam (24.6%).[9,18,21,22] Our study showed lower mean IZD of tetracycline (21.2 mm) compared to Vietnam (24.6 mm).[18]

In our study, the rates of RS to ceftriaxone and cefixime exceeded 5%, the threshold set by the WHO to adjust treatment recommendation.[9,18] However, MIC and categorical resistance of gonococci have been noted to poorly correlate with treatment outcomes.[11,14] Among all six verified treatment failures with ceftriaxone, two cases had gonococci isolates with MIC below the WHO cutoff for ceftriaxone RS (MIC ≥0.125 mg/L), and five cases had

Table 1. Antibiotic susceptibility testing of *Neisseria gonorrhoeae* isolates by disc diffusion

	Participants (N=19)	
Antibiotics	**N (%)**	**Mean IZD, mm (range, mm)**
Ceftriaxone		37.5 (24–48)
Susceptible (≥35 mm)	16 (84.2)	
Reduced susceptibility (<35 mm)	3 (15.8)	
Cefixime		31.1 (6–46)
Susceptible (≥31 mm)	13 (68.4)	
Reduced susceptibility (<31 mm)	6 (31.6)	
Azithromycin		34.2 (31–42)
Not resistant (>30 mm)	19 (100.0)	
Resistant (≤30 mm)	0 (0.0)	
Tetracycline/doxycycline		21.2 (18–25)
Susceptible (≥38 mm)	0 (0.0)	
Intermediate (31–37 mm)	0 (0.0)	
Resistant (≤30 mm)	19 (100.0)	

IZD, inhibition zone diameter.

pharyngeal infection.[6] In a study by Cole et al, six participants were not cleared of infection despite having gonococci isolates susceptible to both ceftriaxone and azithromycin. Three of these participants had pharyngeal and rectal infections. The difference in azithromycin pharmacokinetics in extragenital sites might account for the failure.[14] In contrast, Ko et al reported a case of pharyngeal gonorrhoea in Singapore with ceftriaxone-resistant (MIC 1 mg/L) and azithromycin-susceptible (MIC <0.25 mg/L) isolate, which was successfully treated with ceftriaxone and azithromycin.[23] Despite the unclear association of in vitro resistance and treatment outcome, our results suggest a possible risk of treatment failure and emergence of untreatable gonococcal infection if cephalosporin monotherapy is used for gonorrhoea in Indonesia.[14,19] Our study also revealed resistance to tetracycline in all and resistance to azithromycin in none of the gonococci isolates. These results supported the currently used dual regimen of cephalosporins and azithromycin as first-line treatment for gonorrhoea in our setting. These results also imply that doxycycline is unsuitable for the treatment of gonorrhoea but might be considered in cases of coinfection with chlamydia.[4,10] The wide variation in the antibiotic resistance rate between our study and those of other centres highlights the importance of routine surveillance of antimicrobial resistance and adjustment of treatment guidelines according to the local susceptibility patterns.[24]

Our study also shows that there was a higher percentage of *N. gonorrhoeae* isolates with RS and smaller IZD for ceftriaxone and cefixime in MSM participants compared to heterosexual participants. Similar findings have been reported in the United States and the Netherlands.[6,25]

Our study has some limitations. It included only male participants, the sample size was small and it used disc diffusion for antibiotic susceptibility testing. The gold standard for antibiotic susceptibility testing is determination of the MIC using agar dilution. However, studies have reported good agreement between disc diffusion and agar dilution (93.1%–100%) as well as the ETEST (bioMérieux, France) for ceftriaxone (93.0% agreement) and cefixime (92.1% agreement). Disc diffusion is also a simpler and cheaper method that has comparable accuracy to agar dilution.[24,26,27] Therefore, this method can be used as an alternative in resource-limited settings, such as in Indonesia.[26,27]

Conclusion

The antibiotic resistance or RS of *N. gonorrhoeae* was highest with doxycycline followed by cefixime and ceftriaxone. No resistance was observed against azithromycin. A dual treatment regimen with ceftriaxone and azithromycin can still be recommended as the first-line therapy for gonorrhoea in Indonesia. Doxycycline is not suitable for gonorrhoea but can be considered for coinfection with chlamydia. Local surveillance of the antibiotic susceptibility of *N. gonorrhoeae* with a larger sample size including both male and female participants would be valuable. Future AMR studies can be improved by using agar dilution and the ETEST method.

Table 2. Antibiotic susceptibility testing of *Neisseria gonorrhoeae* isolates by disc diffusion according to sexual orientation of the participants

	MSM (N=6)		Heterosexual (N=13)	
Antibiotics	**N (%)**	**Mean IZD, mm (range, mm)**	**N (%)**	**Mean IZD, mm (range, mm)**
Ceftriaxone		37.2 (30–43)		37.6 (24–48)
Susceptible (≥35 mm)	4 (66.7)		12 (92.3)	
Reduced susceptibility (<35 mm)	2 (33.3)		1 (7.7)	
Cefixime		22.8 (6–38)		34.9 (25–46)
Susceptible (≥31 mm)	2 (33.3)		11 (84.6)	
Reduced susceptibility (<31 mm)	4 (66.7)		2 (15.4)	
Azithromycin		32.5 (31–34)		34.9 (31–42)
Not resistant (>30 mm)	6 (100.0)		13 (100.0)	
Resistant (≤30 mm)	0 (0.0)		0 (0.0)	
Tetracycline/doxycycline		21.3 (19–25)		21.1 (18–24)
Susceptible (≥38 mm)	0 (0.0)		0 (0.0)	
Intermediate (31–37 mm)	0 (0.0)		0 (0.0)	
Resistant (≤30 mm)	6 (100.0)		13 (100.0)	

IZD, inhibition zone diameter; MSM, men who have sex with men.

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Competing interests: None.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

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