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Ceftriaxone-and-cefixime-resistant *Neisseria gonorrhoeae* in a 26-year-old-male with gonococcal urethritis: a case report

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ABSTRACT

Introduction: Gonorrhoea is the most prevalent sexually transmitted infection (STI) in Indonesia. The increasing resistance of *Neisseria gonorrhoeae* to antibiotics has prompted the World Health Organization (WHO) to classify gonorrhoea as an urgent public health threat. Reports of resistance to third generation extended-spectrum cephalosporins (ESCs), such as cefixime and ceftriaxone, against *N. gonorrhoeae* are rare in Indonesia. This study aims to present a case of cefixime and ceftriaxone resistance in a 26-year-old man with gonococcal urethritis.

Case Description: A 26-year-old man presented to an STI clinic with a two-week history of increased urethral discharge. He reported a history of sexual activity with multiple partners. Physical examination revealed mucopurulent exudate and thick greenish-white pus from the external genitalia. Microscopic examination of a urethral smear identified numerous polymorphonuclear cells (>10 PMN/high-power field) and Gram-negative intracellular diplococci. Bacterial culture confirmed the presence of Gram-negative diplococci consistent with *N. gonorrhoeae*. Polymerase chain reaction (PCR) testing further confirmed *N. gonorrhoeae*. Susceptibility testing revealed resistance to both cefixime and ceftriaxone. The patient was treated with dual therapy, consisting of a single oral dose of azithromycin (1 g) and cefixime (400 mg). Complete symptom resolution was achieved within one week.

Conclusion: Third-generation ESCs, including injectable ceftriaxone and orally administered cefixime, are the most commonly used antibiotics for gonorrhoea treatment. Resistance to these drugs represents a significant global health threat. Discrepancies between antibiotic susceptibility test results and clinical outcomes highlight the need for further investigation into underlying factors contributing to treatment efficacy.

Keywords: cefixime, ceftriaxone, gonococcal urethritis, *Neisseria gonorrhoeae*.

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INTRODUCTION

Gonorrhoea is classified as a highly communicable sexually transmitted infection caused by the bacterium *Neisseria gonorrhoeae*. The World Health Organization (WHO) estimated that 82.4 million new infections with *N. gonorrhoeae* occurred among adults aged 15 to 49 years globally in 2020.¹ Young adults are considered at higher risk of developing gonorrhoea due to increased sexual activity associated with their physical and mental development, often combined with a lack of awareness regarding safe sexual practices.² In China, Zeng et al. reported that between January 2016 and December 2020, the annual incidence of gonorrhoea in Zhejiang Province increased steadily,

ranging from 22.73 to 39.65 cases per 100,000 individuals, with an average annual incidence of 30.50 cases.³

In Indonesia, gonorrhoea has been documented as the most prevalent sexually transmitted infection (STI). Studies conducted in Surabaya, Jakarta, and Bandung indicated that the prevalence of gonorrhoea among female sex workers (FSWs) ranged from 7.4% to 50%. Data from the Ministry of Health in 2018 reported 63,815 cases of gonorrhoea nationwide, which increased to 73,027 cases in 2019. The 2018 Integrated Biological and Behavioral Survey by the Ministry of Health revealed that the highest prevalence was among men who have sex with men (MSM) at 17.8%, followed by transgender individuals (8.6%) and female

sex workers (11.4%).⁴

The global prevalence of gonorrhoea, coupled with the rapid development of antibiotic resistance by *N. gonorrhoeae*, has been recognized by the WHO as an urgent public health threat. According to the WHO Gonococcal Antimicrobial Surveillance Program (GASP), antibiotic resistance has been reported across Asia, North America, Europe, Latin America, the Caribbean, Africa, and Australia. Data from 60 countries in 2016 indicated resistance rates to extended-spectrum cephalosporins (ESCs), such as ceftriaxone and cefixime, at 30%, azithromycin at 49%, ciprofloxacin at 95%, and penicillin and tetracycline at 39.6%.⁵

The spread of infectious diseases and antibiotic resistance remains a growing



Figure 1. Mucopurulent discharge in the external genitalia.

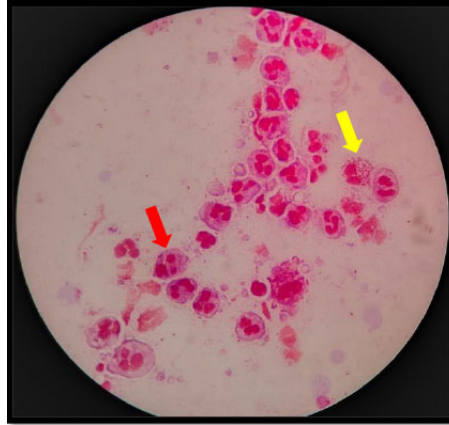


Figure 2. A Gram staining of urethral swab shown Gram-negative intracellular diplococci (yellow arrow) and polymorphonuclear cells (red arrow).

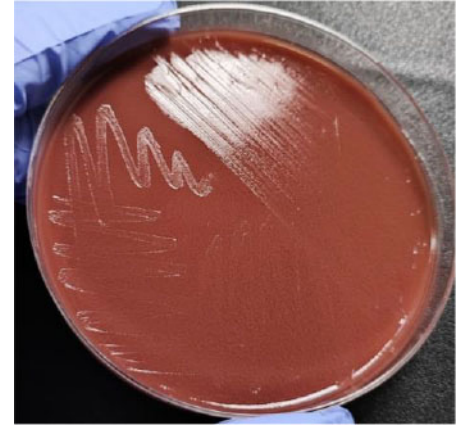


Figure 3. Sub cultured *N.gonorrhoeae* in Chocolate Agar: Greyish-white, transparent to opaque colony.

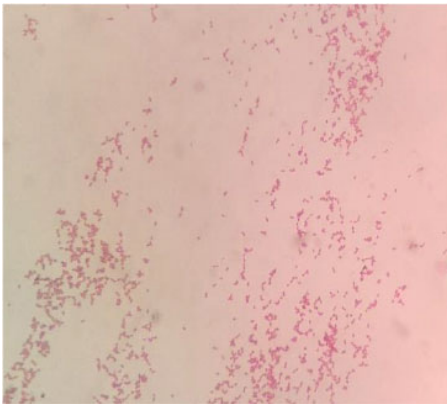


Figure 4. Gram staining of *N.gonorrhoeae*.

global health concern, exacerbated by increased human mobility. In Indonesia, studies on *N. gonorrhoeae* resistance have highlighted alarming trends. Research conducted in 2011 at RSUP Dr. M. Djamil Padang revealed resistance rates of 73.1% to cefixime, 53.8% to ceftriaxone, and varying resistance to other antibiotics, including levofloxacin (73.1%) and kanamycin (23.1%).⁶ A more recent study in 2020 by Lita et al. at RSSA Malang found that 19.23% of *N. gonorrhoeae* isolates were resistant to cefixime, and an equal percentage were resistant to ceftriaxone.^{6,7}

The emergence of resistance to third-generation extended-spectrum cephalosporins (ESCs), such as cefixime and ceftriaxone, and the identification of *N. gonorrhoeae* strains exhibiting high-level clinical resistance to all ESCs, represent a significant concern.⁸ In Indonesia, ESCs, including ceftriaxone and cefixime, are the standard treatment for gonorrhoea.

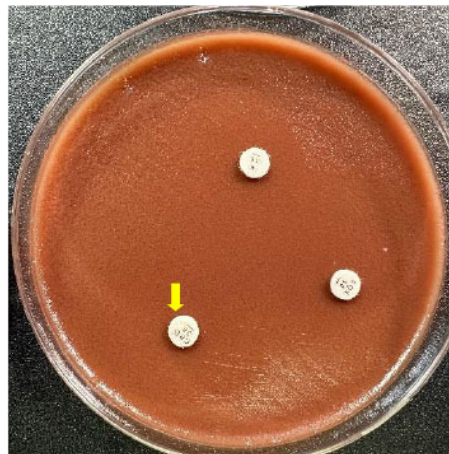


Figure 5. Antibiotic susceptibility test of ceftriaxone (yellow arrow) and cefixime (red arrow) using Kirby–Bauer disk diffusion method in chocolate agar.

Table 1. The result of antibiotics susceptibility test

Antibiotics	Zone Diameter of Inhibition (mm)	Interpretation (CLSI, 2023)
Penicillin	20	R
Ceftriaxone	30	R
Cefoxitin	30	S
Cefotaxime	35	S
Cefepime	30	S
Cefixime	20	R
Tetracycline	15	R
Ciprofloxacin	17	R

However, the fastidious nature of *N. gonorrhoeae* complicates culture and phenotypic antibiotic susceptibility testing. As a result, cases of resistance to ESCs are infrequently reported in Indonesia. This report describes a case of cefixime and ceftriaxone resistance in a 26-year-old man diagnosed with gonococcal urethritis.

CASE DESCRIPTION

A 26-year-old male patient presented to an STI clinic with complaints of increased urethral discharge persisting for two weeks prior to admission. The discharge was described as odorless, thick, and slightly greenish-white, accompanied by dysuria characterized by pain and a stinging

sensation during micturition. No fever, itching, pelvic, or abdominal pain was reported. The patient disclosed a history of unprotected sexual intercourse three weeks before the onset of symptoms and had been sexually active for one year. He reported multiple sexual partners, including three girlfriends, but was unaware of any history of sexually transmitted infections (STIs) among them. He also had no history of circumcision. On physical examination, vital signs were within normal limits, with a blood pressure of 134/76 mmHg, pulse rate of 99 beats per minute, and a body temperature of 36°C. Examination of the external genitalia revealed mucopurulent exudate and thick greenish-white pus (Figure 1).

Following counseling, two urethral swab samples were aseptically collected. Microscopic examination of Gram-stained smears showed numerous polymorphonuclear cells (>10 PMN/high-power field) and Gram-negative intracellular diplococci (Figure 2). The swab samples were immediately streaked onto Thayer-Martin and chocolate agar plates and incubated overnight at 37°C in 5% CO₂. After incubation, greyish-white, transparent to opaque colonies, slightly raised and approximately 1 mm in diameter, were observed. These colonies were subsequently sub-cultured onto chocolate agar (Figure 3). Gram staining of the colonies revealed pink to red diplococci with kidney bean-shaped cells opposing each other on their concave sides (Figure 4), confirming the presumptive identification of *Neisseria gonorrhoeae*.

For definitive confirmation, polymerase chain reaction (PCR) was performed on another urethral swab sample at the Microbiology Department, Faculty of Medicine, Universitas Gadjah Mada, using the RT-PCR Bio-Rad CFX 96° system. Forward and reverse primers targeting the *N. gonorrhoeae* *porA* pseudogene (5'-CGGCTCGTTTATCGGCTT-3' and 5'-ATCGGTATCACTCGCTCTGC-3') were utilized. The result was positive for *N. gonorrhoeae* with a CT value of 23.77. Based on these findings, a diagnosis of gonococcal urethritis was established.

Antibiotic susceptibility testing of the recovered isolates was conducted using the Kirby-Bauer disk diffusion method

(Figure 5), and results were interpreted according to CLSI 2023 guidelines. The isolate demonstrated resistance to penicillin, tetracycline, cefixime, ceftriaxone, and ciprofloxacin, while susceptibility to cefoxitin and cefotaxime was noted (Table 1).

The patient was treated with dual therapy, consisting of a single oral dose of azithromycin (1 g) and cefixime (400 mg). Complete symptom resolution was achieved within one week, indicating successful treatment.

DISCUSSION

Neisseria gonorrhoeae is a nonmotile, aerobic, Gram-negative diplococcus bacteria with a diameter of around 0.8 µm. It has a kidney bean-like shape, with the flat or concave sides being next to each other when the organisms are found in pairs. *N. gonorrhoeae* attack the mucous membranes of the genitourinary tract, eyes, rectum and throat which can produce acute suppuration. *N. gonorrhoeae* colonization causes symptoms due to the influx of neutrophils to the site of infection.^{9,10} In men, urethritis usually occurs with white or yellowish cream pus and pain when urinating. The process can continue to the epididymis and if not treated properly, fibrosis and urethral stricture can occur.¹¹ In this case, the symptoms of patient were greenish-white pus discharge from the external genitalia and pain when micturition. He also had a history of sexual activity with multi partner. Urethral swabs sample were aseptically obtained and microscopic examinations showed numerous polymorphonuclear cells (>20 PMN/high-power field) and Gram-negative intracellular diplococci.

Culture examination on chocolate agar revealed greyish-white, transparent to opaque colonies that were slightly raised and approximately 1 mm in diameter. Gram staining of these colonies demonstrated pink to red diplococci with kidney bean-shaped cells positioned opposite each other on their concave sides. Confirmation using polymerase chain reaction (PCR) detected the presence of *N. gonorrhoeae*. Diagnosing gonococcal infections remains challenging and requires a combination of diagnostic techniques, including direct smear microscopy, culture, and nucleic

acid amplification tests (NAATs).¹² Among these, culture is still recommended for phenotypic antibiotic susceptibility testing.

Antibiotic susceptibility testing using the Kirby-Bauer disk diffusion method revealed resistance to penicillin, tetracycline, cefixime, ceftriaxone, and ciprofloxacin, while cefoxitin, cefotaxime, and cefepime showed susceptibility (Table 1). The zone diameter and interpretation of inhibition breakpoints were assessed according to CLSI 2023 guidelines. Based on these results, it was established that the *N. gonorrhoeae* strain causing urethritis in this patient was resistant to both cefixime and ceftriaxone. Extended-spectrum cephalosporins (ESCs), such as the injectable ceftriaxone and orally administered cefixime, are among the most commonly used antibiotics for treating gonorrhoea. Cephalosporins function by inhibiting peptidoglycan cross-linking in the bacterial cell wall through binding to penicillin-binding proteins (PBPs). However, resistance to these ESCs is increasingly being reported.⁸

To adapt and survive under selective pressure, *N. gonorrhoeae* utilizes a variety of resistance mechanisms acquired and developed through evolution.⁸ Resistance to broad-spectrum cephalosporins, such as cefixime and ceftriaxone, has been associated with polymorphisms in several genes, particularly certain *penA* mosaic alleles. The *penA* gene encodes penicillin-binding protein 2 (PBP2), which is critical for cell wall synthesis. Additional genetic alterations, such as mutations in the *mtrR* efflux pump system that enhance antimicrobial efflux, and *penB* mutations affecting an outer membrane porin protein, also contribute to resistance.¹³

In this case, dual therapy was initiated with a single oral dose of azithromycin (1 g) and cefixime (400 mg). Complete recovery was achieved, with the patient reporting resolution of symptoms within one week. Despite resistance to cefixime noted in the antibiotic susceptibility testing, clinical recovery was observed. The discrepancy between antibiotic sensitivity test results and clinical outcomes can be influenced by multiple factors. Technical variables in the laboratory, such as inoculum size, media composition and depth, timing of

disk application, incubation conditions (temperature, atmosphere, and duration), antibiotic concentration on the disk, bacterial generation time, and zone measurement techniques, may all affect the reliability of the Kirby–Bauer disk diffusion method.¹⁴ This case underscores the complexity of treating *N. gonorrhoeae* infections, particularly in the context of emerging resistance, and highlights the importance of integrating clinical judgment with laboratory findings for effective management.

Apart from technical factors, the presence or absence of bacterial virulence factors are also important determinants of patient outcomes regardless of the sensitivity profile of the antibiotic chosen for management. The presence or absence and the level of expression of virulence determining factors are aspects that are not considered in in vitro susceptibility testing.¹⁵ This patient was also given the oral azithromycin in addition to cefixime, but due to our limitation, we could not carry out susceptibility testing for azithromycin. In this study, we also found some difficulties for cultivating the bacteria in Thayer Martin agar. That limitation also made we couldn't conduct AST according to CLSI guidelines, and we can only conduct disc diffusion tests on chocolate agar. The finding of AST results in this case must be tested again in another referral laboratory, which could not be done due to the unavailability of this kind of laboratory

CONCLUSION

In this report, a case of gonococcal urethritis in a 26-year-old male patient was described. The diagnosis was established based on the patient's history, clinical findings, direct microscopic examination, bacterial culture, and PCR results. Antibiotic sensitivity testing revealed that the causative agent, *N. gonorrhoeae*, was resistant to cefixime and ceftriaxone. Resistance to these drugs represents a significant global health threat and warrants close monitoring. The observed discrepancies between antibiotic

susceptibility test results and the clinical outcome highlight the influence of various factors, which require further investigation and analysis.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

PATIENT'S INFORMED CONSENT

This article has obtained patient consent for publication.

AUTHOR CONTRIBUTION

Conceptualization, methodology and writing original draft preparation: Nuryastuti T, Susetiati D. A; Formal analysis: Prameshwara AA; Data curation: Prameshwara AA, Prawarni VP; Validation: Nuryastuti T, Susetiati D. A; Writing, review and editing: Prameshwara AA; Approval of final manuscript: all authors.

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