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2023 Korean Association of Urogenital Tract Infection and Inflammation guidelines for gonococcal infection

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The incidence of gonorrhea has increased significantly in recent years in the United States, especially among sexually active twenty-year-olds. Although the incidence of gonorrhea has decreased in Korea since the early 2000s, it is still common among people in their twenties. Nucleic acid amplification test (NAAT) is the most sensitive diagnostic test for detecting gonococcal infection. Gram-staining is a simple and useful laboratory test for diagnosing symptomatic male gonococcal urethritis. Although bacterial culture can be used to detect antimicrobial susceptibility, its sensitivity is lower than that of NAAT. Treatment for uncomplicated gonorrhea infection is a single intramuscular injection of ceftriaxone 500 mg. Doxycycline (100 mg twice daily for 7 days) is added if there is a possibility of co-infection with chlamydia. If ceftriaxone is difficult to use, spectinomycin 2 g can be injected intramuscularly in Korea. Patients with gonorrhea should have repeated examinations within three months at the exposure site because of a high risk of re-infection. A person diagnosed with gonorrhea should discuss the nature of the infection, the importance of informing partners, when sexual activity can resume, and how to reduce the risk of sexually transmitted infections.

Keywords: Guideline; *Neisseria gonorrhoeae*; Sexually transmitted diseases

INTRODUCTION

Gonorrhea was the most common bacterial sexually transmitted infection (STI) in Korea until 2006. Although its incidence has decreased, it is still most commonly reported in sexually active people in their 20s [1,2]. Unlike Korea, a rapid increase in the incidence of gonorrhea has been confirmed in the United States (US) since 2013 especially among sexually active people between ages of 20 and 29 [3]. This infection is caused by *Neisseria gonorrhoeae*, a Gram-negative diplococcus. It can be transmitted sexually or through the vagina to the fetus during childbirth Gonorrhea can cause urethritis and epididymitis in males, and cervicitis and endometritis in females. If not treated properly, it can lead to infertility in both males and females. Recent increases in antimicrobial resistance to gonorrhea have changed the

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Centers for Disease Control and Prevention (CDC)'s treatment recommendations for gonorrhea [4]. Currently, the only drug recommended for gonorrhea treatment in the US is ceftriaxone. However, in the case of infectious diseases, antibiotic resistance varies by region. Thus, it is important to create guidelines tailored to each region. Previously, Korean STI guidelines have played an important role in the Korean healthcare system by providing evidence-based recommendations tailored to domestic epidemiological and clinical practices. This review aims to evaluate Korean STI guidelines for gonococcal infection by summarizing evidence to date. It also aims to update key recommendations with their rationales and implementation. Ultimately, this review aims to improve clinical decision-making and promote optimal patient care for individuals affected by gonococcal infection in Korea.

DEVELOPMENT OF KOREAN GUIDELINES

The Korea Centers for Disease Control and Prevention (currently the Korea Disease Control and Prevention Agency [KDCA]) and the Korean Association of Urogenital Tract Infection and Inflammation (KAUTII) developed the first STI guideline (2011) in 2009–2010 and revised it later in 2016. Six years after that, in 2022, the KDCA and the KAUTII carried out the second revision of the guideline from July 2022 to April 2023.

The development committee consisted of a steering committee, a development committee, a writing committee, an internal review committee, and an external review committee. The writing committee included an insurance team for insurance-related review, just like the first revision of the guideline. The external review committee consisted of the Korean Urological Association, Korean Society of Obstetrics and Gynecology, (direct erection system) Korean College of Obstetrics and Gynecology, Korean Society of Laboratory Medicine, Korean Society of Clinical Microbiology, Korean Society of Infectious Diseases, and Korea Centers for Disease Control and Prevention. There was no conflict of interest from the beginning of development to the end of development.

Following the recommendation of Clinical Practice Guideline Executive Committee of the Korean Medical Association (KMA), we took the form of local adaptation to accommodate and develop foreign guidelines to suit the Korean situation. Therefore, various databases including PubMed, NICE, KoreaMed, Trials registers (clinicaltrials.gov), SciELO, Scopus, Embase, Google Scholar, Cochrane Library, National Guideline Clearinghouse, and CMA Infobase: Clinical Practice Guidelines Database were used to search existing treatment recommendations for acceptance development. Search index words for STI was "sexually transmitted infection" OR "sexually transmitted disease". Treatment guideline index words was "guideline" OR "national guideline" OR "practice guideline" OR "management guideline" OR "consensus" OR "recommendation". The range of publication dates was from January 2017 to December 2022. The latest edition was selected if there was a revision. Ten foreign STI guidelines were searched by topic or format.

After excluding guidelines that were not developed based on evidence or published without references, we evaluated five guidelines, including guidelines of the World Health Organization (WHO) and CDC in the US, guidelines of the British Association for Sexual Health and HIV (BASHH) in the United Kingdom (UK), guidelines of the International Union Against Sexually Transmitted in Europe, and guidelines of the Japanese Society for Sexually Transmitted Infections in Japan. For quality evaluation, the K-AGREE 2.0 (Korean version of AGREE 2.0) evaluation development scale distributed by the Clinical Practice Guideline Expert Committee of the KMA was used. Four members of the development committee evaluated six areas to obtain standardized scores for each area. After comparing these scores of each area, two guidelines (CDC and WHO) were finally selected with the standardization score for development rigor and the score for applicability of 50% or higher.

To adapt to the domestic situation, domestic data were searched and analyzed in all fields. Key questions were derived using the Population or Patient problem, Intervention, Comparison, Outcome (PICO) formulation. For literature search, PubMed (https://www.pubmed.gov) and KoreaMed (https://www.koreamed.org) were used. Papers published in Korean were first searched. In case of lack of evidence, evidence was selected by re-searching without limiting the publication year. We excluded systematic review and meta-analysis with low level of evidence and case reports. The Delphi technique was applied to derive and adopt recommendations for the draft. A total of 17 panels were formed to ensure representativeness and expertise of the recommendation.

DIAGNOSIS

Diagnosis of gonococcal infection varies from traditional bacterial culture to recent nucleic acid amplification tests (NAATs). Gram-staining as another non-culture test can diagnose urethral gonococcal infection in symptomatic males. Bacterial culture is recommended when antimicrobial

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resistance is a concern, especially when treatment failure is suspected.

1. Nucleic acid amplification test

NAAT is the most sensitive test to detect gonococcal infection [5]. Although NAAT cannot confirm antibiotic susceptibility of gonorrhea, research on this is in progress [6]. The biggest problem with NAAT is the false positive result caused by detecting residual nucleic acid of contaminated strain or dead bacteria. For this reason, when using the NAAT as a test-of-cure, care must be taken in determining the timing and result of the test.

2. Gram-staining

Gram-staining is frequently performed for males with purulent urethral discharge. Diagnosis can be made by identifying intracellular Gram-negative diplococci. When an appropriate sample is obtained, Gram-staining has a sensitivity of 95% or more and a specificity of 99% or more [7]. However, it is not recommended for males with asymptomatic urethral infections or for specimen obtained from other sites due to a low sensitivity [4]. The sensitivity of microscopy is the highest in male urethral slides, reaching 89%. However, it drops to 51% and 54% for endocervical and rectal smears, respectively [8].

3. Bacterial culture

Bacterial culture is a standard test for the identification of gonorrhea. However, it is not often used these days because its sensitivity is low due to the need for a special environment for transportation and culture. It is mainly used for monitoring antibiotic resistance [4].

4. Specimen

In males, first urine and urinary swab samples are suitable for diagnostic testing. NAAT (e.g., real-time polymerase chain reaction [PCR]) can be performed for first urine. Gram-staining, bacterial culture, and NAAT can be performed for a urinary swab sample. In females, swabs can be performed from the endocervix or vagina. Both bacterial culture and NAAT are possible. However, vaginal swab specimens are not suitable for culture because of the presence of commensal *Neisseria*. Gram-staining is less sensitive in females then in males. Thus, it is not generally recommended [4]. Urine samples are less sensitive than vaginal swabs in females [9].

TREATMENT

Recently, the CDC's recommendations for gonorrhea treatment have changed significantly [4]. Main changes are: (1) ceftriaxone dose is increased; and (2) azithromycin is not routinely recommended as additional therapy (Table 1).

1. Ceftriaxone monotherapy

Azithromycin 1 g was added to the recommended regimen for gonococcal infections in 2015 for the successful treatment of gonococcal infections with reduced susceptibility to ceftriaxone and for preventing the emergence of resistance [10]. However, evidence suggesting a synergistic effect between cephalosporin and azithromycin *in vitro* is inconclusive [11-13]. Recently, the prevalence of azithromycin resistance has increased worldwide, including Korea. High levels of azithromycin-resistant *N. gonorrhoeae* have been reported in many countries around the world [14-19]. Although some ceftriaxone-resistant isolates have been reported to be susceptible to azithromycin, a 1 g dose might be insufficient to clear a gonococcal infection [20]. In a randomized controlled trial by Ross et al. [21] in 2019, combined treatment of gentamicin 240 mg IM and azithromycin 1 g eliminated infection in only 91% of participants. It did not show non-inferiority to ceftriaxone 500 mg. This suggests that a 1 g dose of azithromycin is insufficient for treating gonorrhea. Another reason to avoid azithromycin in treating gonorrhea is antibiotic stewardship in sexual health. This is because using azithromycin for treating gonorrhea can accelerate the induction and spread of resistance in other STI infections, especially *Mycoplasma genitalium* and *Treponema pallidum*.

2. Dose of ceftriaxone

Ceftriaxone is a third-generation cephalosporin with variable pharmacokinetics. Efficacy is best predicted by the duration of the time when the concentration of free (i.e., unbound) drug in blood remains higher than the minimal inhibitory concentration (MIC) of gonococcal bacteria [22]. There are no human data to determine the time to maintain concentrations above the MIC required to clear gonorrhea from various anatomical sites. Using Monte Carlo modeling, it has been estimated that ceftriaxone should have a concentration higher than the MIC of gonorrhea for about 20–24 hours for effective treatment of urogenital gonorrhea [22]. Ceftriaxone 250 mg dose does not reliably maintain levels higher than MIC≥0.125 μg/mL for a sufficient period of time [22]. Connolly et al. [23] have estimated pharmacokinetic and pharmacodynamic parameters required for treating genitourinary gonorrhea against susceptible and resistant strains of *N. gonorrhoeae* in a murine model. The lowest ceftriaxone dose (MIC=0.008 μg/mL) effective for eradicating 100% of susceptible organisms after 48 hours of treatment was 5 mg/kg body weight, which

Table 1. Guidelines for treating gonococcal infection

Disease condition	Recommendation	Alternative
Uncomplicated urethral/cervical/rectal gonorrheal infection in adults/adolescents	Ceftriaxone 500 mg IM/IV (<100 kg) or 1 g IV (≥100 kg) in a single dose	1. Spectinomycin 2 g IM in a single dose 2. Gentamicin 240 mg IM in a single dose PLUS azithromycin 2 g orally in a single dose
Uncomplicated adult/adolescent gonococcal infection of the pharynx	Ceftriaxone 500 mg IM/IV (<100 kg) or 1 g IV (≥100 kg) in a single dose	None
Gonococcal infection in pregnant females	Ceftriaxone 500 mg IM/IV (<100 kg) or 1 g IV (≥100 kg) in a single dose	None
Gonococcal conjunctivitis	Ceftriaxone 500 mg IM/IV (<100 kg) or 1 g IV (≥100 kg) in a single dose	
Disseminated gonococcal infections	Ceftriaxone 1 g IM or by IV every 24 hours (for a minimum 10 days)	1. Cefotaxime 1 g by IV every 8 hours (for a minimum of 10 days) 2. Ceftizoxime 1 g every 8 hours (for a minimum of 10 days)
Uncomplicated gonococcal vulvovaginitis/cervicitis/urethritis/pharyngitis/proctitis in infants/young children (body weight≤45 kg)	Ceftriaxone 25–50 mg/kg body weight by IV or IM in a single dose, not to exceed 250 mg IM	
Prevention of ophthalmia neonatorum	Erythromycin (0.5%) ophthalmic ointment for each eye in a single application at birth	
Treatment of ophthalmia neonatorum	Ceftriaxone 25–50 mg/kg body weight by IV or IM in a single dose, not to exceed 250 mg IM	When ceftriaxone cannot be used due to concurrent administration of intravenous calcium, cefotaxime 100 mg/kg body weight by IV of IM as a single dose

IM, intramuscular injection; IV, intravenous injection.

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corresponded to fT>MIC of 23.6 hours, consistent with Monte Carlo simulation results [23]. Converting this to a human dose, 500 mg of ceftriaxone corresponds to 5 mg/kg of body weight in a person of 80 to 100 kg, while 250 mg of ceftriaxone corresponds to 3 mg/kg of body weight. Although ceftriaxone-resistant strains with MIC>0.125 mg/L have not been reported in Korea yet, the distribution of ceftriaxone MICs has increased (i.e., with an increase of reduced susceptibility) [17]. Ceftriaxone-resistant *N. gonorrhoeae* strains have already been identified worldwide including the UK [14,15,24,25]. Although low-dose ceftriaxone might be suitable for treating most gonococcal species, high-dose ceftriaxone is more effective for most isolates with increased MICs than low dose [23]. Therefore, the recommended dose of ceftriaxone was increased to 500 mg for adults weighing less than 100 kg and to 1 g for adults weighing more than 100 kg to successfully treat the strain with reduced susceptibility (Fig. 1). Intramuscular injection is thought to be helpful in maintaining concentrations above the MIC for more than 24 hours due to the "depot effect" [26]. In the US FDA approval label of ceftriaxone (https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50585s057,50624s027lbl.pdf), there is no significant difference in 24-hour plasma concentration between intramuscular and intravenous injections. Therefore, when the MIC breakpoint of the susceptibility of gonorrhea to ceftriaxone is 0.125 or 0.25 μg/mL, intravenous administration does not seem to be less effective than intramuscular administration. Moreover, intramuscular injection of ceftriaxone can cause pain, which most patients complain about. In the past, when intramuscular injection of 250 mg ceftriaxone was recommended, pain was not greatly considered. However, when its dose was increased to 500 mg or 1 g, the pain could not be ignored. Ceftriaxone 500 mg should be dissolved in 2 mL of 1% lidocaine hydrochloride solution and injected deep into buttocks [27].

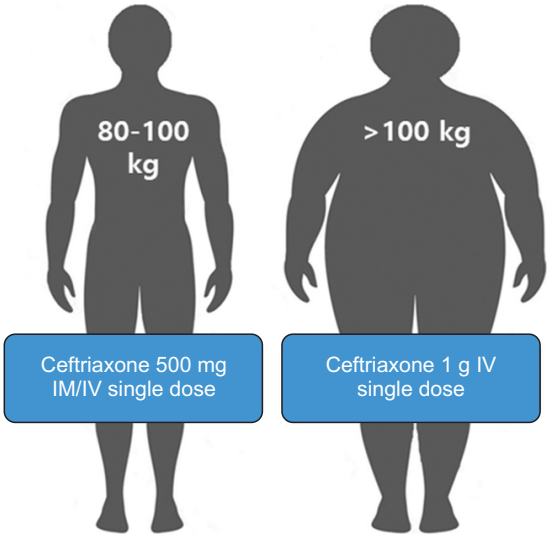

Fig. 1. Ceftriaxone dosage based on body weight for uncomplicated urethral/cervical/rectal gonorrheal infection in adults/adolescents. IM, intramuscular injection; IV, intravenous injection.

3. Alternative therapy: Gentamicin plus azithromycin

A large randomized controlled-trial has investigated the efficacy and safety of gentamicin for treating gonorrhea [21]. In that study, gentamicin was used in combination with 1 g of azithromycin. Microbiological cure (negative NAAT after 2 weeks of treatment) was achieved in 94% of urogenital infections, 90% of rectal infections, and 80% of pharyngeal infections [21]. Another randomized trial has used a 2 g dose of azithromycin in combination with gentamicin [28]. Although gonococcal infection was 100% eliminated in that study, its objectives included very few non-genital infections, which was insufficient to provide a reliable estimate of the efficacy of this treatment regimen for rectal or pharyngeal infections [28]. In particular, when using 2 g of azithromycin, gastrointestinal adverse reactions (mainly vomiting within 1 hour after administration) occurred in 3%–4% of patients treated with gentamicin and azithromycin. These patients required re-treatment with ceftriaxone and azithromycin. Nevertheless, gentamicin plus azithromycin therapy can be considered as an alternative to ceftriaxone for cephalosporin-allergic patients with genital gonococcal infections. Since spectinomycin is available in Korea, it is recommended as an alternative therapy to ceftriaxone. In a previous meta-analysis study, cure rates of spectinomycin and ceftriaxone were not significantly different (82.6% vs. 88.0%, p=0.05) [29]. According to results of analysis of antimicrobial resistance of gonorrhea in Korea, strains resistant to spectinomycin were not observed in 2017 or 2018 [30]. Gentamicin plus azithromycin or spectinomycin is less effective for non-genital infections, especially pharyngeal gonococcal infections than for urogenital gonococcal infection [31]. Thus, it is not recommended.

4. Alternative therapy: Cefixime

The 800 mg oral dose of cefixime should only be considered as an alternative therapy to cephalosporins because it does not provide as high or sustained blood bactericidal levels as ceftriaxone 500 mg IM [32]. It also shows limited efficacy for treating of pharyngeal gonorrhea (81% cure, 95% confidence interval 61%–92%) [33]. In particular, sensitivity of gonorrhoeae isolated in Korea to cefixime decreased from 91% in 2018 to 77% in 2019 [30]. Cefixime susceptibility decreased significantly from 2014. Proportions of non-suscep-

tible strains based on Clinical & Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing were 15% and 31% in 2017, 9% and 32% in 2018, and 23% and 47% in 2019, respectively [30]. Changes in MIC of cefixime might reduce the effectiveness of cefixime in treating genitourinary gonorrhea. In addition, continued use of cefixime might promote the development of resistance to ceftriaxone. Other oral cephalosporins (e.g., cefpodoxime and cefuroxime) are not recommended for treating gonorrhea due to their inferior potency and less favorable pharmacodynamics than ceftriaxone or cefixime [34,35].

FOLLOW-UP AND MONITORING

For people with uncomplicated gonococcal infections of the cervix, urethra, or rectum, routine test-of-cure is not recommended. However, follow-up for one to two weeks after treatment is necessary. If symptoms persist despite proper treatment or if there is a risk of re-infection, a test-of-cure is necessary. Because a person diagnosed with gonorrhea is at a high risk of reinfection, such person is recommended to undergo a repeat test within three months. However, this should be regarded as a test for re-infection, not for confirmation of cure [4].

If pharyngeal gonorrhea infection is treated, a test-of-cure is required on days 7–14. If PCR result for test-of cure is positive, bacterial culture is essential to find resistant strains. In gonococcal infection occurs during pregnancy, a test-of-cure must be performed after treatment. When performing a test-of-cure using NAAT, it should be performed at three weeks after the end of treatment to prevent false positive results [4].

Patients with gonococcal infection must be counseled to notify their partners. All partners who had sexual contact within 60 days from the date of diagnosis are advised to undergo testing. Persons being treated for gonorrhea infection should avoid sexual activity for at least 7 days after completing treatment and until all genitourinary symptoms have disappeared. Sexual partners should have appropriate testing and treatment for gonorrhea and avoid sexual activity until at least 7 days have elapsed after receiving treatment.

FURTHER RESEARCH

Ceftriaxone is an important antibiotic used to treat *N. gonorrhoeae* infections. However, recent emergence of ceftriaxone-resistant strains of *N. gonorrhoeae* has raised deep concerns. The first case of ceftriaxone-resistant *N. gonorrhoeae* was reported in Japan in 2009 [36]. Since then reports of resistance have been increasing in many regions of the world, including Asia, Europe, and North America [37,38]. Ceftriaxone is currently the only antibiotic recommended by the WHO as the primary treatment for gonorrhea due to its superior efficacy and low cost [4]. The emergence of resistance to ceftriaxone is raising concerns about the effectiveness of current treatment options, highlighting an urgent need for alternative treatments. There is also an urgent need for continued research, surveillance, and public health interventions to prevent and control the spread of resistant strains.

Although vaccines against gonorrhea have been studied before, effective vaccines are not available yet. This is because many structures of the gonococcal outer layer tend to change rapidly, making it difficult for the human immune system to recognize. The correlation between human immunological protection against gonorrhea is unknown [39]. Nonetheless, gonorrhea vaccination using the 4CMenB vaccine at a sexual health clinic in the UK has suggested a cost-effective possibility [40]. Although many challenges remain to be overcome, the development of a vaccine could be paramount to success of achieving WHO's goal of reducing the incidence of gonorrhea by 90% by 2030.

CONCLUSIONS

Gonorrhea is a global health problem. Its incidence is increasing again recently. Although the emergence of ceftriaxone-resistant gonococci has not been reported in Korea yet, its worldwide spread has been reported. Treatment strategy for gonorrhea in the era of antibiotic resistance is to administer high-dose of ceftriaxone. It is also important to develop new alternative methods. Efforts to treat gonorrhea patients and their partners and to establish a surveillance system for antibiotic resistance are needed.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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