Overview article

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Antimicrobial resistance and associated gene mutations of *Neisseria gonorrhoeae*

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Abstract

Neisseria gonorrhoeae is the causative agent of gonorrhea, a globally prevalent sexually transmitted infection, and was classified by the World Health Organization (WHO) in 2024 as a high-priority bacterial pathogen. The current first-line treatment includes third-generation broad-spectrum cephalosporins (ceftriaxone or cefixime) as monotherapy and/or combined with azithromycin. The increasing resistance to these first-line antibiotics has led experts to include *N. gonorrhoeae* in this priority list.

N. gonorrhoeae has developed resistance to multiple antibiotics, including penicillins, cephalosporins, azithromycin, fluoroquinolones, and tetracyclines. The emergence and spread of multidrug-resistant strains, which show reduced susceptibility to broad-spectrum cephalosporins and azithromycin, pose a significant global health threat. Resistance mechanisms in *N. gonorrhoeae* are diverse, and studies have shown that specific mutations influence resistance to cephalosporins and macrolides in key genes. Timely detection of resistant strains and their associated resistance mechanisms is crucial for improving treatment strategies and monitoring the antimicrobial susceptibility profile of *Neisseria gonorrhoeae*.

Keywords: *Neisseria gonorrhoeae*; sexually transmitted infections; antimicrobial resistance; mutation.

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1. INTRODUCTION

Neisseria gonorrhoeae is a Gram-negative diplococcus and the causative agent of gonorrhea, a common sexually transmitted infection affecting both men and women. According to the World Health Organization (WHO), an estimated 82.4 million new cases of gonorrhea were reported worldwide in 2020 [1]. Infections with *N. gonorrhoeae* are often asymptomatic, particularly in women, and many cases are only diagnosed and treated after complications such as cervicitis, pelvic inflammatory disease, or ectopic pregnancy have developed. Although gonorrhea is not fatal, it can have serious consequences for reproductive health, potentially leading to infertility in both men and women. Various antibiotics, including penicillins, tetracyclines, cephalosporins, fluoroquinolones, and macrolides, have been used to treat gonorrhea. However, reduced susceptibility to these antibiotics has emerged and is increasingly widespread, diminishing their treatment efficacy [2–4]. Currently, the

recommended first-line treatment in many countries is third-generation broad-spectrum cephalosporins (ceftriaxone or cefixime) as monotherapy and/or combined with azithromycin [2–4].

In recent years, cases of cephalosporin resistance have emerged [5–8]. They are spreading, particularly with the rise of multidrug-resistant strains that show reduced susceptibility to broad-spectrum cephalosporins and azithromycin. The increasing antimicrobial resistance in *N. gonorrhoeae* has become a global health threat, leading the WHO to classify it as a high-priority pathogen in 2024 [9]. Resistance mechanisms in *N. gonorrhoeae* are diverse, and studies have shown that specific mutations influence resistance to cephalosporins and macrolides in key genes. Timely detection of resistant strains and their associated resistance mechanisms is crucial for improving treatment strategies and monitoring the antimicrobial resistance profile of *N. gonorrhoeae*.

2. REVIEW

2.1. Worldwide burden of gonorrhea

WHO has recognized gonorrhea as a significant public health issue and has implemented infection management programs and enhanced surveillance of antimicrobial resistance in *N. gonorrhoeae*. In 2020, WHO estimated 82.4 million new cases of gonorrhea among adults globally [1]. The highest incidence rates were reported in the WHO African Region, followed by the Americas and the Western Pacific, and the lowest in the European Region [10]. In 2023, the United States reported 601,319 cases of gonorrhea, ranking second after chlamydia in terms of new infections, with half of the cases occurring among men who have sex with men [11]. In Vietnam, according to statistics from Can Tho Dermatology Hospital in 2020, *N. gonorrhoeae* accounted for 12% of all sexually transmitted infections (STIs) and remains one of the leading causes of genital infections among patients seeking medical care [12].

The WHO strategy aims to reduce the number of new gonorrhea cases among individuals aged 15–49 to 8.23 million annually by 2030, achieving a 90% reduction in incidence [13]. A systematic review of European epidemiology from 1949 to 2021 showed a decline in genital *N. gonorrhoeae* infections by approximately 3% annually [9]. However, this rate of decline is still slow compared to the WHO's target of a 90% reduction by 2030. Notably, in recent years, high rates of *N. gonorrhoeae* infections have been observed among men who have sex with men, with infections occurring in the anorectal and oropharyngeal regions. The proportion of gonorrhea cases involving oral and anal sex reported in the WHO surveillance program in 2023 was 35% and 36%, respectively [14]. The increasing trend of infections through anal and oral sex raises concerns about the emergence of new drug-resistant strains, as *N. gonorrhoeae* may recombine with commensal *Neisseria* species in the oropharynx, potentially acquiring genetic elements associated with antimicrobial resistance.

2.2. Antimicrobial resistance (AMR) of *N. gonorrhoeae*

The global health threat posed by gonorrhea is becoming increasingly severe as the level of antimicrobial resistance in *N. gonorrhoeae* continues to rise and spread. Since the introduction of antibiotic therapy

for gonorrhea, *N. gonorrhoeae* has rapidly developed resistance to these drugs. Various antibiotics, including penicillins, cephalosporins, tetracyclines, fluoroquinolones, spectinomycin, and macrolides, have been recommended for treatment at different times as the bacterium's susceptibility to antibiotics has shifted. Older antibiotics such as penicillin, tetracycline, and fluoroquinolones were once effective in treating gonorrhea, but they have now lost their utility due to the high prevalence of resistant strains. Almost all *N. gonorrhoeae* strains isolated from new cases each year are resistant to one or more of these antibiotics.

Currently, broad-spectrum cephalosporins such as ceftriaxone or cefixime are the first-line choices for empirical monotherapy of gonorrhea [13]. However, the emergence and spread of resistance to these cephalosporins are concerning. Reduced susceptibility or resistance to ceftriaxone has been reported since 2015, and the first treatment failure with cefixime was documented in Japan [15]. According to WHO reports, resistance to ceftriaxone increased from 0.8% in 2022 to 4% in 2023, while resistance to cefixime rose from 1.7% to 9% [16]. In addition to monotherapy, dual therapy combining ceftriaxone or cefixime with azithromycin is also recommended. In 2016, the first treatment failure for oropharyngeal gonorrhea with ceftriaxone and azithromycin was confirmed in the UK. Since then, treatment failures with ceftriaxone alone or in combination with azithromycin or doxycycline have been reported in multiple countries. According to the WHO Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP), antimicrobial resistance rates in 2023 were higher than in 2022, with Vietnam and Cambodia being the only countries reporting resistance to ceftriaxone and having the highest rates of resistance to cefixime and azithromycin [17]. In Vietnam, resistance rates were 20% for ceftriaxone, 30% for cefixime, and 7% for azithromycin [18]. This poses a significant concern for empirical antibiotic therapy and underscores the importance of gonococcal surveillance programs.

Several factors contribute to the rising antimicrobial resistance in *N. gonorrhoeae*. In addition to factors related to antibiotic use, such as unrestricted antibiotic use, inappropriate selection and administration of antibiotics, and non-adherence to treatment, one notable characteristic of *N. gonorrhoeae* is its ability to undergo genotypic and phenotypic changes by acquiring new genetic material through conjugation or transformation. In antimicrobial resistance, a clear example is the acquisition of plasmids encoding penicillinase production, which confers resistance to penicillin [19]. These plasmids can spread rapidly through conjugation, leading to the global dissemination of penicillin-resistant *N. gonorrhoeae* [16]. In addition to plasmid-mediated resistance, the accumulation of chromosomal mutations in *N. gonorrhoeae* also contributes to increased resistance. Chromosomally mediated resistance typically emerges and spreads more slowly than plasmid-mediated resistance, as it requires time to accumulate sufficient mutations to produce phenotypic changes [16]. The rise in extragenital *N. gonorrhoeae* infections, such as in the throat, anus, and rectum, may

also play a significant role in the development of resistant strains, as *N. gonorrhoeae* can interact and exchange genetic material with other bacteria in these sites.

2.3. Gene mutations causing AMR in *N. gonorrhoeae*

N. gonorrhoeae develops antibiotic resistance through mechanisms that reduce the drug's access to its target site, including:

1. Reducing membrane permeability: This occurs through changes in porin proteins on the bacterial membrane, limiting the entry of antibiotics into the cell.

2. Active efflux pumps: The bacterium can produce pumps that actively expel antibiotics from the cell, preventing them from reaching their target.

3. Enzyme secretion: *N. gonorrhoeae* can secrete enzymes that degrade or modify antibiotics before they reach their target site.

Additionally, *N. gonorrhoeae* can alter or eliminate the target sites of antibiotics on the cell. Genetically, these changes can occur through chromosomal mutations or acquiring resistance genes via plasmids. Multiple resistance determinants can coexist in a single bacterial strain, leading to progressively higher resistance levels and enabling the strain to simultaneously resist multiple classes of antibiotics.

2.3.1. Penicillin and cephalosporin resistance

Penicillin was widely used to treat gonorrhea starting in the 1940s. However, reports of penicillin-resistant *N. gonorrhoeae* emerged in the 1970s. The era of penicillin ended with the appearance of *N. gonorrhoeae* strains producing penicillinase were first reported in 1976. Introducing second and third-generation cephalosporins, including ceftriaxone and cefixime, proved highly effective in treating gonorrhea. However, by 2012, second-generation cephalosporins were removed from the first-line treatment recommendations by the U.S. Centers for Disease Control and Prevention (CDC) due to rising minimum inhibitory concentrations (MICs) and numerous treatment failures [20], [21]. Currently, third-generation cephalosporins such as ceftriaxone and cefixime are recommended as first-line treatments for gonorrhea [2], [22]. Nevertheless, resistance to these antibiotics has been increasing. Resistance to penicillin and cephalosporins occurs through two primary mechanisms:

1. Chromosomally-mediated resistance (CMRNG): This mechanism involves mutations in the *penA* gene (encoding penicillin-binding protein [PBP-2]), the *mtr* locus (encoding efflux pump proteins that expel antibiotics from the cell), and the *penB* gene (encoding porin proteins in the cell membrane).

2. Penicillinase-mediated resistance (PPNG): This mechanism involves the expression of β-lactamase enzymes encoded by plasmid genes. Currently, this mechanism is limited to resistance against penicillins and tetracyclines. The spread of this resistance occurs through plasmid conjugation, allowing horizontal gene transfer within microbial communities and leading to widespread resistance from an initial strain [23], [24]. This mechanism facilitates faster dissemination of resistance compared to chromosomally-mediated resistance.

In clinical case reports, ceftriaxone-resistant *N. gonorrhoeae* strains have been found to carry mosaic mutations in the

penA gene. Most recently, a systematic review and meta-analysis by Mendes A. C. et al. (2024) reported that over 50% of penicillin-, ceftriaxone-, and cefixime-resistant strains harbored mutations in the *penA* and *mtrR* genes [25]. In Japan, Shu-ichi N. et al. (2016) documented variants of the ceftriaxone- and multidrug-resistant FC428 strain, which carried mutations at positions A311V and T483S [26], consistent with strains previously reported in Japan and Australia. In Vietnam, Phạm Thị Loan et al. (2024) identified the two most common mosaic variants as *penA*-273.001 (in Hanoi and Ho Chi Minh City) and *penA*-60.001 (primarily in Ho Chi Minh City) [27]. These mosaic *penA* variants consistently featured mutations at A311V, V316T/P, and T483S.

These findings highlight the evolving nature of antibiotic resistance in *N. gonorrhoeae* and underscore the need for continued surveillance and novel treatment strategies to combat this growing public health threat.

2.3.2. Tetracycline resistance

Tetracycline has been commonly used to treat gonorrhea, particularly in countries with limited healthcare resources due to its low cost. Tetracycline inhibits bacterial protein synthesis by targeting the 30S ribosomal subunit. The emergence and spread of tetracycline-resistant *N. gonorrhoeae* (TRNG) have been closely monitored since it was first reported in the United States in 1985. The increasing prevalence of *N. gonorrhoeae* strains with reduced susceptibility to tetracycline has led to frequent treatment failures.

Chromosomal mutations and the acquisition of resistance genes via plasmids are the primary mechanisms of tetracycline resistance. Chromosomal mutations involve amino acid substitutions, such as Val57Met or Val57Leu, in the S10 protein encoded by the *rpsJ* gene. These mutations affect tetracycline's ability to bind to and inhibit bacterial protein synthesis. Additionally, the acquisition of plasmids carrying the *tetM* determinant (first reported in the United States in 1986) has led to the formation and rapid spread of tetracycline-resistant strains. The tetM protein binds to the 30S ribosomal subunit, preventing tetracycline from attaching to its target site. The *tetM* plasmid is widely distributed among normal genital tract microbiota [28], [29]. The mobility of these plasmids and the selective pressure from using tetracycline to treat other sexually transmitted infections have contributed to the widespread dissemination of TRNG phenotypes. Another study by Trinh Minh Trang et al. on 114 strains of *N. gonorrhoeae* in Vietnam (from 2019 to 2020) noted that 14 strains harbored the rpsJ:V57M mutation, which relates to tetracyclin resistance, and no strain had a tetM plasmid mutation [30].

2.3.3. Fluoroquinolone resistance

Resistance to quinolones is primarily mediated by chromosomal mutations that affect cell membrane permeability and efflux pump mechanisms. High-level resistance is often associated with mutations in the *gyrA* gene, which encodes DNA gyrase, a primary target of quinolones. Additionally, mutations in the *parC* gene, which encodes topoisomerase IV—a secondary target of quinolones—are also linked to high-level resistance. Changes in *parC* typically arise when mutations affect *gyrA*, which also appeared in strains from Vietnam. The increasing

prevalence of ciprofloxacin resistance has led to its removal from treatment recommendations in many countries. This underscores the need for ongoing surveillance and alternative treatment strategies to address the growing challenge of quinolone-resistant *N. gonorrhoeae*.

2.3.4. Macrolide resistance

Macrolide antibiotics inhibit protein synthesis by binding to the 50S ribosomal subunit, preventing the translocation of peptidyl-tRNA and blocking peptide exit from the 50S subunit through interaction with 23S rRNA. This results in the release of incomplete polypeptide chains. Azithromycin, a macrolide, has shown significantly higher efficacy in treating gonorrhea compared to erythromycin. Resistance to azithromycin was first reported in the late 1990s in Latin America. Over time, the prevalence of azithromycin resistance has increased: a 2016 evaluation of *N. gonorrhoeae* antibiotic susceptibility in 25 European countries revealed a resistance rate of 7.5%, slightly higher than the 7.1% reported in 2015 (though not significantly different) [31]. By 2022, the resistance rate to azithromycin had risen to 9% (with a MIC threshold > 1 μg/ml), a change considered "significant" compared to 2016 [32]. Current treatment guidelines recommend azithromycin in combination with ceftriaxone or cefixime as part of dual therapy [2], [22]. The mechanisms of azithromycin resistance involve alterations in the ribosomal target, including:

1. Methylase-related rRNA modifications: These changes reduce the binding affinity of macrolides to the ribosome.

2. Polymorphisms in the peptidyl transferase region of 23S rRNA: Mutations in this region can confer resistance.

3. Increased efflux pump activity: Enhanced expression of efflux pumps, particularly the MtrCDE efflux system and pumps encoded by *mef* and *MacAB* genes, actively expel azithromycin from the bacterial cell [33].

2.3.5. Aminoglycoside resistance

Spectinomycin and aminoglycosides are commonly used to treat gonorrhea in many developing countries due to their cost-effectiveness [34]. Resistance to spectinomycin and aminoglycosides typically arises through chromosomal mutations, leading to high-level resistance [16]. Various ribosomal genes are involved in resistance to these antibiotics, and their mechanisms are interconnected. However, the slightly elevated MIC (minimum inhibitory concentration) of gentamicin in some isolates suggests that resistance may involve porin-related mechanisms [35]. In the future, aminoglycoside-resistant *N. gonorrhoeae* strains could acquire and express plasmid-encoded resistance genes, further complicating treatment efforts.

2.4. The importance of *N. gonorrhoeae* survey

N. gonorrhoeae is increasingly becoming a "superbug" due to its resistance to multiple antibiotics used in first-line treatment regimens. Recent studies have identified several genes associated with virulence and antibiotic resistance, notably the presence of the *penA*-60.001 allele, which is linked to reduced susceptibility to ceftriaxone and cefixime. Some strains also show reduced susceptibility to azithromycin, threatening the efficacy of current treatments. Given the rising antibiotic resistance, the development of a vaccine against *N. gonorrhoeae* has become a top priority. Researchers are

focusing on identifying bacterial surface antigens to create an effective vaccine. For example, replacing the gonococcal outer membrane protein PorB with meningococcal PorB has been shown to enhance antibody titers and immune responses, offering a promising strategy for gonorrhea vaccine development. A study in New Zealand found that the MeNZB vaccine, initially developed to prevent meningitis caused by *Neisseria meningitidis* group B, reduced gonorrhea incidence by 31% in a study of 14,000 individuals aged 15–30, suggesting cross-protection against gonorrhea [36].

A study at Hanoi Medical University Hospital reported a co-infection rate of 27.78% between *N. gonorrhoeae* and *Chlamydia trachomatis* [37]. Co-infections with other pathogens can lead to more severe complications, complicate diagnosis and treatment, and increase the risk of antibiotic resistance, adverse outcomes for patients, and community transmission. This highlights the importance of simultaneous screening for sexually transmitted infections (STIs). Consequently, research into improved diagnostic tools for *N. gonorrhoeae* is gaining attention. Nucleic acid amplification tests (NAATs), which detect bacterial genetic material, have shown sensitivity and specificity exceeding 95% in urethral and cervical swabs, as well as male urine samples. Advancements in diagnostic tools enable rapid and accurate detection, supporting timely and effective treatment.

The symptoms of gonorrhea not only affect physical health but also cause psychological stress, anxiety, and shame, negatively impacting patients' quality of life. If left untreated, the infection can lead to serious complications such as pelvic inflammatory disease, infertility, and an increased risk of HIV transmission. A study of 1,251 male STI patients at Hanoi Medical University Hospital found that 13.1% had unstable sexual partners, while 84.2% and 71.8% reported inconsistent condom use and oral sex, respectively [38]. Therefore, community education about the risks and prevention of *N. gonorrhoeae* infection plays a crucial role in controlling its spread. In summary, addressing the challenges posed by *N. gonorrhoeae* requires a multifaceted approach, including vaccine development, improved diagnostics, effective treatment strategies, and public health education to reduce transmission and mitigate the impact of this increasingly resistant pathogen.

2.5. Trends in gonorrhea study

In 2024, the World Health Organization (WHO) classified *N. gonorrhoeae* as a high-priority bacterial pathogen [39]. This designation is due to several critical issues, including rising antibiotic resistance and significant public health concerns. The increasing resistance observed in *N. gonorrhoeae* strains globally have been a major driver for this classification. Over time, resistance to first-line antibiotics has steadily risen, and the accumulation of resistance traits in bacteria will eventually lead to a tipping point where "quantity transforms into quality," resulting in a growing number of clinical treatment failures [4], [40]. Therefore, managing antibiotic resistance and identifying related genetic mutations are urgent priorities in controlling gonorrhea. Numerous international projects are underway to analyze genetic mutations, aiming to map

the prevalence and role of specific mutations in *N. gonorrhoeae* strains.

Another critical research focus is the public health risk posed by gonorrhea. Changes in cultural attitudes and sexual behaviors have led to an increase in non-traditional sexual practices. As a result, the manifestations of gonorrhea are becoming more diverse (e.g., oropharyngeal and anorectal infections), necessitating comprehensive screening and management to mitigate community transmission risks. Notably, recent observations indicate that urethritis symptoms resembling gonorrhea may not always be caused by *N. gonorrhoeae* but by other *Neisseria* species, such as *N. meningitidis*. These gaps in understanding are crucial to address for effective gonorrhea management.

In Vietnam, gonorrhea remains one of the leading sexually transmitted infections. Antibiotic susceptibility data for *N. gonorrhoeae* needs to be reported periodically to detect early trends in antibiotic resistance, thereby enabling appropriate monitoring and treatment strategies. Currently, studies on the genetic characteristics and resistance mechanisms of *N. gonorrhoeae* are limited due to technical and cost-related challenges. Given the continuous adaptive evolution of *N. gonorrhoeae*, it is essential to intensify in-depth research to detect emerging variants and new mutations affecting the bacterium's drug resistance early, allowing for timely and effective treatment and monitoring strategies for gonorrhea. Additionally, developing and advancing new diagnostic tools that do not rely on culturing to detect drug-resistant strains rapidly would significantly improve treatment efficacy.

3. CONCLUSION

The emergence of various forms of antibiotic resistance in *N. gonorrhoeae* is often accompanied by the rapid spread of the disease. This is not just an issue for low- and middle-income countries; recent treatment failures have also been reported in higher-income countries. Due to limited surveillance resources in some regions, obtaining comprehensive data can be challenging. The prevalence of antibiotic resistance is likely much higher than currently reported, driven by undetected and silent transmission. This underscores the urgent need for enhanced global surveillance, improved diagnostic tools for the early detection of resistance-associated mutations, and innovative treatment strategies to address the growing threat of antibiotic-resistant gonorrhea. Data from studies on the antibiotic susceptibility of *N. gonorrhoeae* will provide valuable information for clinicians and healthcare policymakers in the collective effort to combat gonorrhea, contributing to improved public health.

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