

Antibiotic-Resistant *Neisseria gonorrhoeae*: A Growing Threat of Multidrug Resistance

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Abstract: The high incidence of *Neisseria gonorrhoeae* (*N. gonorrhoeae*) infection and resistance to antimicrobial treatment is a serious problem global matter. Lots of therapeutic options that have been used before are unable to deal with resistance. This resistance could be due to the development of microbial resistance to first-line treatment and has now demonstrated its ability to develop resistance to broad-spectrum cephalosporins, ceftriaxone, the last remaining option for first-line empiric treatment of gonorrhoea. Coordination to raise awareness for the use of new drug methods is important in persistent infectious reactions to gonorrhoea, which can cause reactions of pelvic inflammatory disease, infertility, and chronic pelvic pain in women; and epididymitis in men. The presence of gonorrhoea can also increase the risk of HIV acquisition and transmission. In this review article, we cover the evolution, origin, and spread of antimicrobial resistance and determinants of resistance (with a focus on broad-spectrum cephalosporins) in *N. gonorrhoeae*, detailing the current situation regarding broad-spectrum cephalosporin-verified treatment failure and future treatment options, and highlighting action are essential to meet the huge public health challenges that arise with the possibility of developing untreated gonorrhoea. One of the causes of the high rate of resistance can be the asymptomatic nature of gonorrhoea and its high virulence. Several methods can be used by the main lines of health in dealing with this case. The importance of being aware of the importance of screening and culture is very important. Counselling the affected partner can be the key to prevention.

Keywords: *Neisseria gonorrhoeae*, gonococcal, antimicrobial resistance, antimicrobial resistance

1. Introduction

Gonorrhoea is one of the most common sexually transmitted infections (STIs), especially among young people ages 15-24 years. Globally, in 2015, over 395,000 cases were reported with an increase of 13% since 2014. In the United States, 820,000 new gonorrhoea cases occur each year, and less than half are detected and reported to the CDC [1]. Incidence has risen at an average of 12% per year since 2008, from 29-81 cases per 100,000 people [2]. Data from the World Health Organization (WHO) in 2008, the highest estimates were in the WHO Western Pacific Region, WHO South-East Asia Region, and WHO Africa Region, consecutively [1]. In 2014, among Indonesian males, the prevalence of gonorrhoea was 7, 7/100,000, leading as the second highest in South-East Asia following Thailand [3]. The development of antibiotic drugs resistant gonorrhoea resistance following the spread of gonococcal fluoroquinolone resistance has become a significant global public health concern. Currently, there is only one CDC recommended treatment option for gonorrhoea: a dual regimen of a single shot of ceftriaxone and an oral dose of azithromycin (AZM) [4]. At least ten countries have reported treatment failures with extended-spectrum cephalosporins (ESCs) [5], [6].

The Centers for Disease Control and Prevention (CDC) reported about 30% of new cases of gonorrhoea each year resistant to at least one drug. Gonococci resistance to ESCs and AZM has been described in Europe and globally. A decrease of resistance to cefixime (CFM) (minimum

inhibitory concentration [MIC]>0.125 mg/L) from 4.7% in 2013 to 2.0% reported by The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) in 2014. Additionally, a mean of AZM resistance (MIC >0.5 mg/L) of 7.9% in 2014 has been described [3]. It is crucial to continuously monitor antibiotic resistance in *Neisseria gonorrhoeae* (*N. gonorrhoeae*) and encourage research and development of new treatment regimens.

2. Etiology

Gonorrhoea is an ancient disease firstly introduced in 1378. The Gram-negative obligate aerobic diplococcus (gonococcus) *N. gonorrhoeae* infects only humans in nature spread by sexual contact or through vertical transmission during childbirth. [7] This microorganism can infect any mucous membrane. Gonococci attach to the host mucosal cells penetrate between subepithelial space. The risk of transmission of *N. gonorrhoeae* from an infected woman to the urethra of her male partner is approximately 20% per episode of vaginal intercourse and increase to 60-80% after four more exposures [8]. It has a distinctive feature developing different mutations to acquire resistance against the antibiotics used in treatment against them [9]. Gonococci have evolved and acquired or developed all known physiological resistance mechanisms to all antimicrobials by several means, (i) enzymatic antimicrobial destruction or modification, (ii) target modification or protection reducing affinity for the antimicrobials, (iii) decreased influx of antimicrobials, and (iv) increased efflux of antimicrobials (Figure 1) [2]. Asymptomatic urogenital infections can be

presented in men and women. Rectal and pharyngeal gonorrhoea, commonly asymptomatic, is mostly identified in men who have sex with men.

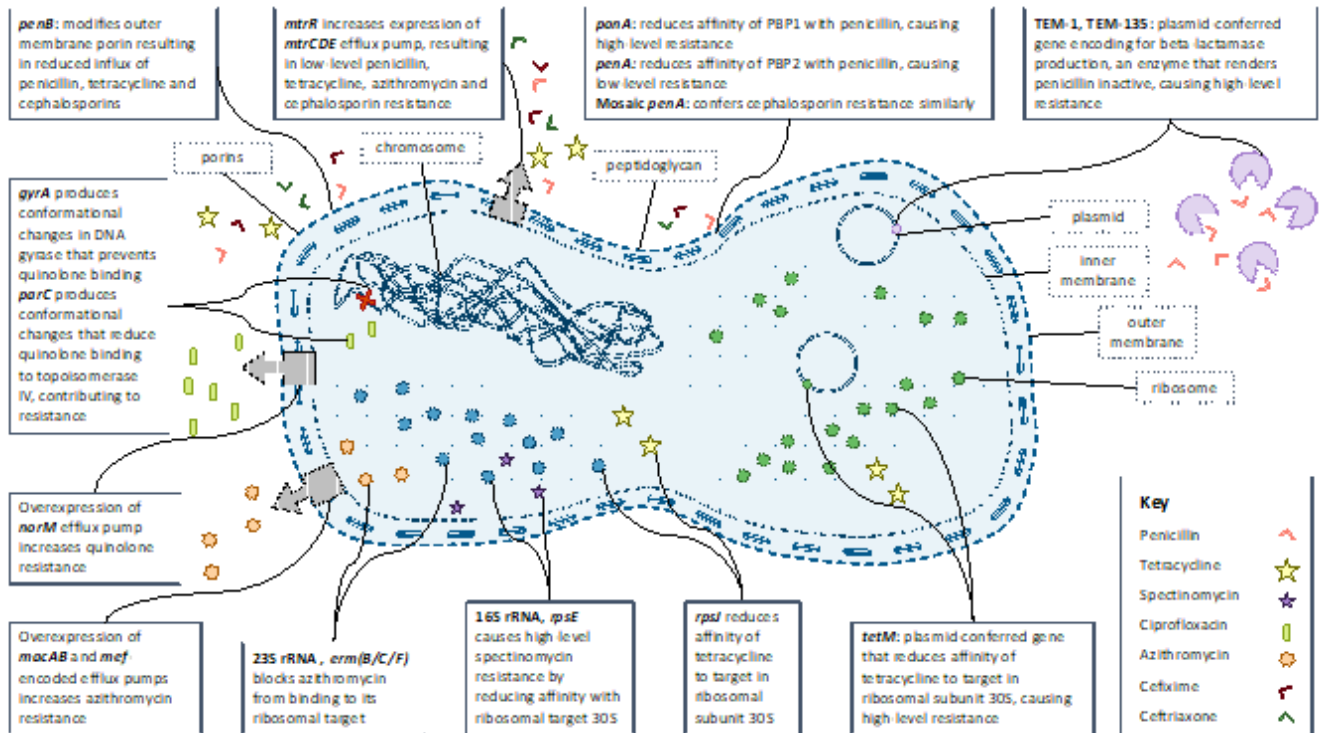


Figure 1: Known mechanisms of resistance in *N. gonorrhoeae* to clinically-relevant antibiotics [5]

Gonococcal infections are considered uncomplicated in the absence of bacteremia or pathogen spread to extragenital sites [10]. Untreated gonorrhoea can cause health problems related to sexual and reproductive health, such as increasing the chances of getting an HIV infection. The infection has the potential to evolve into an ascending infection of the upper genital tract [11]. Urethral strictures secondary to gonococcal infection in men are now less common compared to the antibiotic era. Other rarely found complications in men such as penile lymphangitis, periurethral abscess, and/or acute prostatitis. Permanent sequelae of gonococcal infection in women may lead to infertility, tubal scarring, and/or ectopic pregnancy [9]. Vertical (mother-to-baby) transmission can lead to growth retardation, low birth weight, prematurity, and blindness [12].

3. The Evolution of *Neisseria gonorrhoeae*

Monotherapy is currently not recommended in gonorrhoea treatment as it had a higher chance of developing into antibiotic-resistant gonococcal (ARG). Earlier antibiotics such as quinolones, tetracycline, and penicillin are no longer used in gonorrhoea treatment due to the high resistance found in most gonococcal found globally. Third-generation cephalosporin (ceftriaxone, CFM) currently remains the best option for first-line gonorrhoea treatment, although there is increasing evidence that some gonococcal strains are developing resistance to it. Considering *Chlamydia trachomatis* are also found concomitantly in most gonorrhoea infections, the WHO recommends administering other antibiotics, particularly the macrolide, AZM. By administering a dual therapy concept, it is expected to have better efficacy to thoroughly treat urethritis while also

reducing the chance of antibiotic-resistant microbial development through the different mechanism of action involved [13], [14]. The use of AZM to accompany ceftriaxone is preferred to other alternatives, mainly due to its effectiveness against gonorrhoea as well as the single dose required may increase compliance. Ceftriaxone is considered to have better efficacy in treating oropharyngeal gonorrhoea than CFM [13]-[15].

Table 1: Gonorrhoea treatment recommendation [14], [16].

One of the following		One of the following	
Cefixime 400 mg p. o. (S. D)	AND (+)	Azithromycin 1 g P. O. (S. D)	
Levofloxacin 500 mg p. o (S. D)		Doxycycline 2x100 mg P. O (7 days)	
Ceftriaxone 250 mg I. M (S. D)		Tetracycline 4x500mg P. O (7 days)	
Kanamycin 2 g I. M. (S. D)		Erythromycin 4x500mg P. O (7 days)	
Spectinomycin 2 g I. M. (S. D)			

Gonorrhoea is an ancient disease, well documented from centuries ago. Before the antibiotic age, Gonorrhoea treatment is rudimentary and primarily consists of individual medics' personal experience and opinions. Old treatment includes the use of traditional balsams, urethral irritation, and hyperthermia, along with total sexual abstinence until the symptoms are resolved. During the 19th century, researchers start to look for proper antibacterial agents, leading to the use of some metal such as gold, silver, and mercury as treatment. During the First World War, mercury is often used as a first-line treatment on gonorrhoea patients as well as urethral irrigation [15].

In the present day, these agents are no longer used as treatment options due to their unscientific base along with potentially harmful side effects. The accidental discovery of penicillin antibiotics by Alexander Fleming in 1928 leads to a new era of treating infections. This antibiotic agent is so effective and saved masses of patients from previously fatal infections. However, the first antibiotics to be widely used for gonorrhoea treatment are sulfonamides, found in 1935. Novel antibiotics are continued to be developed as our knowledge of medical technologies widens and deepens with the constant threat of microbial resistance on existing antibiotics [15].

Not long after antibiotics revolutionize gonorrhoea treatment with sulfonamides, gonococcal strains with sulfonamide resistance had been detected in 1944. Penicillin was then discovered to be effective against gonorrhoea and is widely used as sulfonamide replacement since 1943. Sadly, like sulfonamides, penicillin-resistant gonococcal strains are detected in 1960 and exponentially spread until 1976, when β -lactamase producing gonococcal were found. These strains render penicillin to be ineffective and effectively ended the use of penicillin in gonorrhoea patients [14], [15]. Newer antibiotics continued to be developed as time flies tetracycline, spectinomycin, quinolones, and macrolides are the antibiotics proven to treat gonorrhoea effectively [15].

In 1945, tetracycline was developed and used as an alternative to patients with penicillin allergy. However, in the 1980s, a tetracycline-resistant strain are detected and currently is no longer recommended as a gonorrhoea medication worldwide. Spectinomycin is discovered in the 1960s as a gonorrhoea-specific antibiotic. However, not long after, the first case of spectinomycin-resistant gonococcal was reported in 1967, and by 1983, this strain has been reported from the Philippines, South Korea, and England. However, it is concluded that spectinomycin-resistant strain did not develop as fast as other resistant strains and thus, spectinomycin continues to be used as gonorrhoea treatment even today. Spectinomycin is generally not used as a first-line choice for gonorrhoea since its' efficacy in oropharyngeal gonorrhoea is relatively low [15].

The fluoroquinolone antibiotic was discovered by George Leshner in the 1960s and is initially used for uncomplicated urinary tract infections. The fluoroquinolone ciprofloxacin subsequently proved to be a good solution for gonorrhoea during the 1980s and a single dose of 250 mg is widely recommended. Sadly, due to extensive fluoroquinolone use as an empiric choice in many countries, resistant strains of gonorrhoea started to surge, and the recommended therapeutic dose was quickly increased to a single 500 mg dose in the 1990s. Subsequently, the resistance has grown so badly by the 2000s, and thus, the fluoroquinolone role in eradicating gonorrhoea ended abruptly throughout the world [15].

The currently last effective antibiotics recommended for gonorrhoea are macrolides and cephalosporins. The first macrolide found in 1952, erythromycin, is not used for gonorrhoea. It was only when AZM is developed during the 1980s that macrolides become a part of gonorrhoea

treatment. AZM, in particular, had several benefits. Apart from its' effectiveness against gonorrhoea, it expresses inhibitions on other microorganisms, namely *Chlamydia trachomatis*, which is concomitantly found in some gonorrhoea patients [15].

Azithromycin-resistant gonococcal has been reported since the late 1990s, but to date, AZM is still used for gonorrhoea treatment, albeit not as monotherapy due to potential side effects from high dosage and risk of resistance. Cephalosporins are made of the yeast *Cephalosporium acremonium* in 1948 by Giuseppe Brotzu. Numerous novel cephalosporin continues to be developed and the third-generation cephalosporin is the one found with gonorrhoea inhibiting properties. These drugs are very effective and relatively low single doses are sufficient. Globally, 400 mg single dose of CFM is recommended for gonorrhoea, except in Japan, where 300 mg single dose is recommended instead [15].

Just as their predecessor antibiotics, inevitably cephalosporin-resistant gonococcal is first reported in the early 2000s. The appearance of it is probably caused by inadequate dosing resulting in surviving gonococcal developing some resistance. Japan follows it with new guidelines, recommending the use of 1 g intravenous ceftriaxone replacing oral cephalosporins [15]. Between 2006-2011, the MIC of CFM required treat gonorrhoea has increased universally. Oropharyngeal gonorrhoea treatment failure with ceftriaxone has been reported as well in Japan, Australia, and Europe [1]. CDC currently no longer recommends CFM as the first-line choice in gonorrhoea, with ceftriaxone instead gets the approval [17].

In 2018, a case was reported in England, where a patient with gonococcal urethritis and pharyngitis had high resistance to both AZM and ceftriaxone. The patient had a prior history of sexual contact with a local in Thailand. Treatment with doxycycline and spectinomycin also failed, and thus a last resort option of ertapenem was administered before it finally resolved. This report of resistance to not one but two of first-line recommended antibiotics should be worrying about the healthcare community [18]. These gonococcal strains are classed as multidrug-resistant gonococci (MDR-GC) and extensively drug-resistant gonococci (XDR-GC) to describe antimicrobial resistance.

MDR-GC is strained with resistance to one of the two recommended first-line drugs (ceftriaxone/CFM or AZM) along with two other antibiotics. Meanwhile, XDR-GC strains are strains with resistance to both recommended first-line drugs along with at least two other antibiotics [19]. The speeds of new appearing resistant gonorrhoea strains greatly outmatch the speed of newer antibiotics being discovered. The imminent risks of untreatable superbugs are real and posed a very serious threat globally and immediate actions must be taken to stop or at least slow this process.

4. Factor Precipitating The Rise of Resistance

In relation to the surge of resistance, there are few identified factors as listed in **Table 2**.

Table 2: Factor related to the precipitating of resistance

Factor	Explanation	References
Infectious nature	XDR and MDR gonorrhoea are more infectious to healthy persons than their more susceptible strains. Combined with the difficulty of treating these strains, the resistant strains continue to evolve and multiple throughout the world.	[19]
Asymptomatic nature	May appear asymptomatic in most female patients or those with extragenital infections (oropharyngeal, rectal). Asymptomatic patients may still infect their sexual partners unknowingly.	[14], [19]
Highly contagious	Expected that infected men had a 50-60% chance to infect a healthy woman just with a single sexual encounter. In contrast, infected women may have a 20% chance to infect a healthy man in a single sexual encounter.	[19]
History of travel	The individual experiences freedom to exercise otherwise unaccepted or prohibited activities in his place of origin. Homosexual and bisexual populations may have a higher tendency to look for a sexual partner at the destination. All these events led to easier transmission of various gonococcal strains around the world.	[19]
Ignorance	Patients with gonorrhoea did not seek any medical help for a prolonged time. Many factors contributed, including, but not limited, to embarrassment, worried about others' opinions, afraid of a diagnosis, afraid of treatment (particularly invasive ones). In a few cases, the medical professional may also feel uneasy about asking detailed personal questions to the patients or did not suspect any patient's risk.	[19]
Change of guidelines	Gonorrhoea treatment is constantly changing. However, some doctors might not be informed of those changes. Some recommended antibiotics may not be available in certain areas. Thus empiric or alternative therapies are given instead.	[19]

5. Prevention of Antibiotic-Resistant Gonorrhoea

Few preventive steps can be undertaken such as,

- 1) Nucleic Acid Amplification Test (NAAT) - Particularly preferred for asymptomatic patients due to it is a simple and non-invasive procedure, requiring only fresh urine. However, other tests like gram stains, culture, and PCR from various locations (rectal, oropharyngeal) may be exercised if deemed necessary by the examining physician [14], [19].
- 2) Education for safe sex - The patient is encouraged to only have one sexual partner, but should that is not the case, condom usage is strongly recommended to prevent STI transmissions. Sexual partners must be examined and treated as well to prevent reinfection and transmission. Healthcare providers should constantly broaden and update their knowledge according to the latest published guidelines [13], [19].

- 3) Gonorrhoea treatments should be a combination of at least two antibiotics with a different mechanism of action to prevent possible resistance development [13], [19].

6. Conclusion

The number of gonococcal infections is increasing rapidly worldwide. Most worryingly, *N. gonorrhoeae* is an important member of the bacterial community that spreads ARG. A prevention based on the WHO planning needs to take into account the rapidly changing patterns of gonococcal antimicrobial susceptibility. To maintain antimicrobial susceptibility monitoring programs, periodic analysis of susceptibility data, and update treatment guidelines for successful STI/HIV intervention programs. In conclusion, the era of untreated gonorrhoea may be near, which is a serious public health problem. It is imperative to implement action/response plans at global and national levels, focus research and funding on ARG and treatment failure, and promote effective prevention, early diagnosis, and treatment of gonorrhoea.

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