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Review Article

Multi-Drug Resistant Gonorrhea: An Emerging Global Threat

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Abstract

Neisseria gonorrhoeae is the bacterial culprit behind gonorrhea, a highly prevalent sexually transmitted infection (STI) found worldwide. Despite over 1 million daily cases, many infections are asymptomatic, contributing to its widespread transmission. The emergence of multidrug-resistant strains poses a significant challenge to public health, limiting treatment options and increasing the risk of complications. Key aspects covered include the bacterium's transmission dynamics, pathogenesis, clinical manifestations, laboratory diagnosis methods, and epidemiology. Transmission primarily occurs through sexual contact, with the bacterium thriving on mucous membranes in various parts of the body. Clinical presentations range from urethritis and cervicitis to more severe complications such as pelvic inflammatory disease and disseminated gonococcal infection. Laboratory diagnosis relies on culture, nucleic acid amplification tests (NAATs), and Gram staining, with NAATs offering high sensitivity. However, antimicrobial susceptibility testing is essential to guide treatment decisions, given the rapid emergence of resistance. Gonorrhea's epidemiology varies globally, with higher prevalence rates in low- and middle-income countries. Surveillance programs play a crucial role in monitoring antimicrobial resistance trends and informing treatment guidelines. The economic burden of gonorrhea is substantial, with potential increases in medical expenses and the challenge of managing outbreaks. Despite these challenges, there is hope for the development of new treatments and vaccines. Promising candidates such as zoliflodacin and solithromycin have shown efficacy in clinical trials, while vaccine development faces obstacles due to the bacterium's antigenic variation. The paper provides a comprehensive overview of *N.gonorrhoeae,* covering its basic features, transmission, pathogenesis, clinical presentation, laboratory diagnosis, epidemiology, challenges of drug-resistant gonorrhea, and prospects for the development of new treatments and vaccines. The paper underscores the urgent need for continued research, surveillance, and development of effective strategies to combat drug-resistant gonorrhea. Investment in new treatments and vaccines is crucial to mitigate the spread of the infection and its associated complications.

Keywords

N. Gonorrhoeae, Multidrug-Resistance, Gonorrhea, Emerging, Global Threat

1. Introduction

Every day, over 1 million cases of sexually transmitted infections (STIs) are contracted worldwide, with most of them being Asymptomatic. It is estimated that every year, around 374 million new infections of chlamydia, gonorrhea, syphilis, and trichomoniasis occur, with all of them being treatable if diagnosed correctly [1]. Gonorrhea is caused by the bacte-

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rium *Neisseria gonorrhoeae,* its name comes from the Greek words for "seed" and "to flow," referencing the belief that the discharge from the infection contained semen. Gonorrhea has likely been present in humans for thousands of years, as suggested by a passage in Leviticus [2]. It poses a significant public health challenge due to its high prevalence and potential complications if left untreated. Over the years, the treatment of gonorrhea has relied heavily on antibiotics. However, antimicrobial resistance (AMR) to gonorrhoeae has increased over the past 50 years [3].

Multidrug resistance in gonorrhoeae means that the bacteria can resist the effects of various antibiotics, making them unable to treat the infection effectively. This resistance includes commonly used antibiotics like quinolones and early-generation cephalosporins, as well as older antibiotics that used to be last lines of defense against the bacteria. This state of multidrug resistance has led to *N. gonorrhoeae* being referred to as "gonorrhoeae superbugs" or "super gonorrhoeae". This problem has serious consequences for patients and public health in general, as it limits treatment options, extends the infection duration, increases the risk of complications, and boosts transmission rates [4].

The significance of multidrug resistance in gonorrhea lies in its potential to undermine the effectiveness of current treatment regimens and jeopardize the control of this sexually transmitted infection. The World Health Organization (WHO) has identified multidrug-resistant gonorrhea as a global threat, emphasizing the urgent need for research, surveillance, and effective strategies to combat this growing problem [5].

This review will cover various aspects related to *N.gonorrhoeae* including its basic features, epidemiology, drug resistance, diagnosis, development for new treatment and vaccine, and future research implications.

2. *Neisseria Gonorrhoeae*

Neisseriaceae are Gram-negative cocci that are commonly observed in pairs and are known to colonize humans. Only *Neisseria gonorrhoeae* and *N. meningitidis* are pathogenic, with *N. gonorrhoeae* exhibiting unique characteristics that contribute to its virulence. For example, it displays a high degree of antigenic variation in its pili, which aids the bacterium in evading the host immune response and establishing chronic infections. These specialized features of *N.gonorrhoeae,* along with its sensitivity to low temperature and drying, indicate its adaptation to the human host environment. Moreover, its optimal growth conditions at 37 ℃ with humidity and 5-10% CO_2 further demonstrate its specialization for survival and proliferation in the human body [6].

3. Transmission

N. gonorrhoeae is adapted to thrive on mucous membranes found in various parts of the body, including the cervix, uterus, fallopian tubes, urethra [7]. It can also infect the mucous membranes of the mouth, throat, eyes, and rectum. These bacteria have developed ways to stick to and grow on these wet surfaces, leading to infections. However, their inability to endure dry environments and resistance to dehydration makes it impossible for them to survive for extended periods outside the human body. Therefore, the bacterium can only be transmitted via direct contact between mucous membranes or the exchange of contaminated secretions, emphasizing the significance of sexual contact like vaginal, anal, and oral sex in its transmission [8].

Vertical transmission refers to the transmission of *N.gonorrhoeae* from an infected mother to her newborn during childbirth. Gonococcal infection in the newborn can be acquired either in the uterus (following membrane rupture during labour) but more usually through contamination from the birth canal during delivery [9, 10].

Although sexual contact is the primary means of transmission, there is evidence of non-sexual transmission of *N. gonorrhoeae* through epidemics of conjunctivitis, accidental inoculations and fomites [10, 11]. A recent case involved an 8-year-old girl who contracted gonorrhea while in transit on a flight from Rome to Sydney via Moscow. During the flight, the toilets were dirty, and the child used a piece of toilet paper to wipe the seat before using it. It is suspected that the child contracted the disease through auto-inoculation, meaning that the infection was transmitted via her finger while using mixed toilets on a crowded plane. This case highlights the possibility of non-sexual transmission of *N. gonorrhoeae* and further supports the evidence of fomite transmission [12].

4. Pathogenesis

Neisseria strains produce pili that are critical for a range of functions, including host cell attachment, genetic transfer, and motility. In *N. gonorrhoeae,* pili are particularly important for pathogenesis by facilitating attachment to non-ciliated epithelial cells and protecting against neutrophil attacks. The pili are made up of repeating subunits called pilins, which have a conserved region at one end and a variable region at the other that is exposed. The variability in pilin protein and expression hinders the development of effective vaccines for *N. gonorrhoeae* by preventing immunity and complicating efforts to target the bacterium [13].

The outer membrane of Neisseria bacteria has various protein families, including porin proteins that form channels for nutrients and waste products. Only one of the two porin genes i*n N. gonorrhoeae,* called porB, is functionally active and is the most common outer membrane protein. However, developing a vaccine targeting PorB is challenging due to its multiple serologic variants. PorB is essential for *N. gonorrhoeae* virulence because it inhibits neutrophils, aids in bacterial invasion of epithelial cells, and protects against com-

plement-mediated serum killing. Opacity-associated (Opa) are membrane proteins that help *N. gonorrhoeae* attach to different cell types and transmit signals. The number of Opa protein variations varies among different strains and can affect colony appearance, with opaque colonies associated with localized infections and transparent colonies with disseminated infections [13].

The third group of proteins in the outer membrane is the highly conserved Rmp proteins (reduction-modifiable proteins). These proteins stimulate antibodies that interfere with the serum bactericidal activity against pathogenic neisseriae. Lipo-oligosaccharide is an endotoxic antigen composed of lipid A and an oligosaccharide, and other important gonococcal proteins include IgA protease and beta-lactamase. The Fbp iron-binding protein is expressed when the supply of iron is restricted, such as during human infections. Finally, *N. gonorrhoeae* has an active capacity for varying the surface structure's antigenic profile, which enhances its capacity for immune evasion [7, 13].

N. gonorrhoeae can exist both inside and outside of the host's cells. After initial infection, the bacterium forms micro-colonies on specific epithelial cells. Once the colony has reached a certain size, the bacterium attaches to the CD4 receptor on the host cell surface using type IV pili structures. Some bacteria retract their pili through PilE depolymerization, allowing for closer contact between the bacterium and host cells. Opa proteins also bind to CEACAM receptors, inducing rearrangement of the host cell's cytoskeleton and promoting bacterial engulfment. This results in transcellular transcytosis and release of the bacterium into the subepithelial layer. Por proteins help protect the bacterium by inhibiting phagolysosome fusion in phagocytes, thus preventing intracellular killing of the bacterium [7].

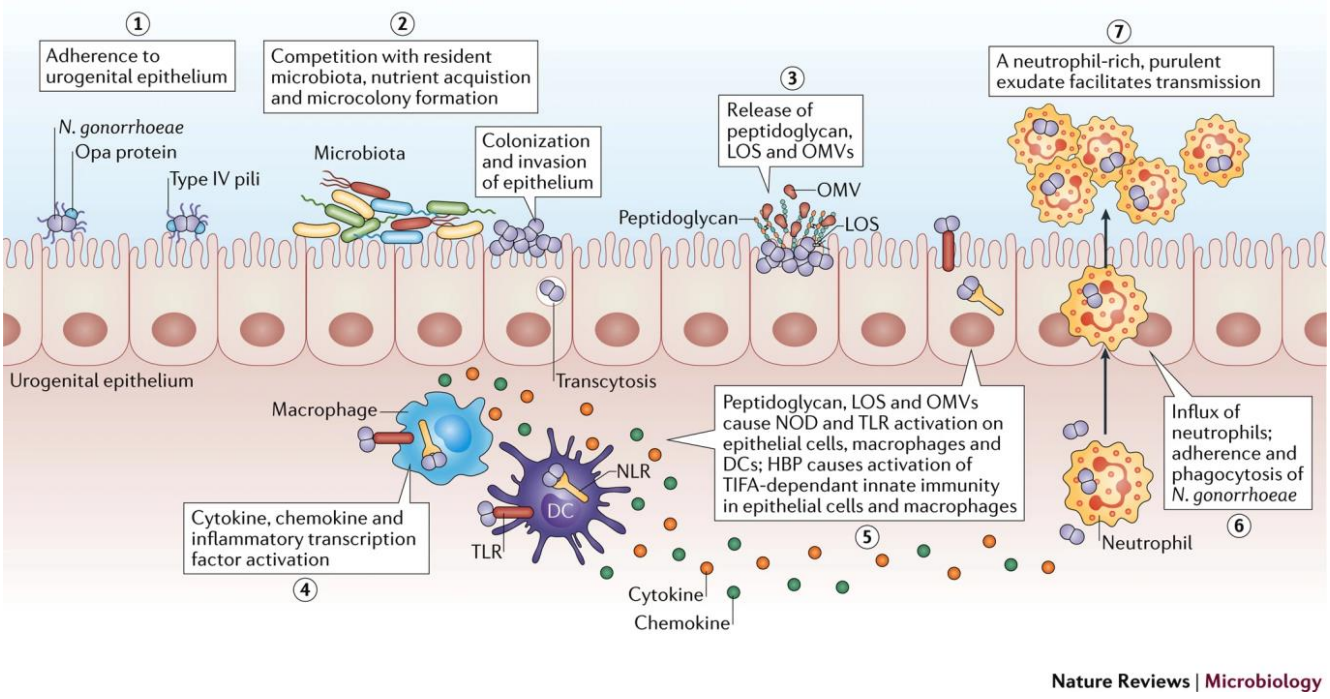

Figure 1. *Overview of Neisseria gonorrhoeae infection [7].*

The host response is characterized by infiltration with leukocytes, followed by epithelial sloughing, formation of micro-abscesses in the submucosa, and production of purulent pus. The LOS of gonococcal cell wall stimulates the production of tumor necrosis factor alpha (TNF-a) and other inflammatory responses which contribute to most of the symptoms associated with gonococcal infection (Figure 1) [14].

5. Clinical Presentation

Genital infections are the most common *N. gonorrhoeae* infections. Uncomplicated gonococcal infection commonly manifests as urethritis in men with symptoms of urethral discharge and dysuria [15]. However, atypical and milder symptoms may also present. Rare complications from gonococcal urethritis include penile lymphangitis, penile edema, periurethral abscesses, and post inflammatory urethral strictures. Epididymitis can also occur as a complication of gonorrhea. Unilateral testicular pain and swelling are common complaints, often accompanied by urethritis [16]. There are also studies indicating that gonorrhea increases the chance of prostate cancer [17].

Gonorrhoea is often asymptomatic in women; less than half of infected women complain of non-specific symptoms. Cervicitis is the most common with symptoms including

vaginal pruritus, mucopurulent discharge, and intermenstrual bleeding. Urethritis is typically asymptomatic but may present with dysuria and urinary urgency or frequency. Pelvic inflammatory disease (PID), affects approximately 10 to 20% of females with cervical gonorrhea, including endometritis, salpingitis and tubo-ovarian abscess, which can lead to ectopic pregnancy and infertility [15, 16].

In rare cases, *N. gonorrhoeae* can cause disseminated gonococcal infection (DGI). This occurs when the bacteria spreads from the initial site of infection through the bloodstream. The incidence of DGI is estimated to be between 0.5 to 3 percent and may be caused by host and microbial factors. DGI often presents as purulent arthritis or a triad of tenosynovitis, dermatitis, and polyarthralgias. Other rare manifestations of DGI include endocarditis, meningitis, and osteomyelitis [16].

Gonococcal conjunctivitis is more common in infants born to untreated mothers, but it can also occur in adults and adolescents through self-infection or outbreaks. The infection can spread through nonsexual contact, fomites, or vectors like flies. Symptoms can range from mild to severe, and if left untreated, the infection can lead to blindness through corneal ulceration and perforation. In Ethiopia, there are reports of 1.18% blindness, with 80% of the cases attributed to preventable or treatable causes. However, there is no clear information on the proportion of the 80% caused by gonorrhea [18]. Additionally, there have been reports of up to 10,000 cases of blindness caused by opthalmia neonatorum, a type of gonococcal infection affecting infants [19].

Non-gonococcal urethritis (NGU) Chronic urethritis where gonococci cannot be demonstrated has been labeled as non-gonococcal urethritis. NGU is more common than gonococcal urethritis. Several agents are implicated in NGU such as *Chlamydia trachomatis*, *Mycoplasma genitalium* [20].

6. Laboratory Diagnosis

Diagnostic specimens for *N. gonorrhoeae* include urethral swabs for males with urogenital symptoms, self or clinician-collected vaginal swabs for females with urogenital symptoms, pharyngeal and rectal swabs for MSM with a history of unprotected anal or oral sex, first-catch urine samples in males and females for initial microbiologic diagnosis, and endocervical swabs as an alternative specimen for NAAT if a speculum exam is already being performed [16].

N. gonorrhoeae can be diagnosed using culture, nucleic acid amplification tests (NAATs) or Gram stain. NAATs are highly sensitive and can be used on various samples, including urine, swabs from the vagina, cervix, and urethra. However, some NAATs may yield false positives due to cross-reaction with other Neisseria species. Culture is specific and less expensive, but has lower sensitivity [15]. Gonococci are very demanding and fastidious pathogens. They do not tolerate dehydration and should be inoculated immediately after swab collection onto culture media [21]. Cultures for *N. gonorrhoeae* are processed on Thayer-Martin agar, which prevents the overgrowth of other endogenous flora [16].

Gram stain can provide a presumptive diagnosis in symptomatic men, but only 50-70% of asymptomatic infections in men are detected and it is less reliable in women. Antimicrobial susceptibility testing should be conducted because NAATs cannot provide this information. A negative Gram stain or culture cannot rule out gonorrhea. In cases of suspected treatment failure, both culture and susceptibility testing should be performed. Gram stain is recommended for symptomatic men with urethritis, but not for detection of cervical, rectal or pharyngeal infection. Methylene blue or Genital Violet stain can be used as an alternative to Gram stain in symptomatic men [15].

Rapid diagnostic tests (RDTs) are essential for detecting *N. gonorrhoeae* in countries with limited laboratory facilities. Microscopy can be used, but it requires trained personnel and may not be sensitive enough. Antigen-detection RDTs are not specific or sensitive for N. gonorrhoeae, while PCR-based RDTs such as GeneXpert CT/NG, Truelab Realtime micro PCR, Randox STI multiplex array, and binx io platform provide reliable results at the point of care, but some are expensive and require electricity. Isothermal amplification-based RDTs, like those using RPA and paperfluidic devices, offer a low-cost alternative with high sensitivity and specificity. The development of microfluidic and nanotechnology-based RDTs, known as lab-on-a-chip systems, has the potential for sensitive and rapid detection of Ng and other diseases [21].

Antimicrobial susceptibility testing is essential to determine the appropriate antimicrobial therapeutic agent for treating *N. gonorrhoeae*. The testing measures the minimum inhibitory concentration (MIC) of an antimicrobial agent required to inhibit growth. Several breakpoint standards are used to assess susceptibility, including CLSI and EUCAST, and testing is performed using the agar dilution method, MIC gradient strip test, or disc diffusion assay. The MIC gradient strip test method is currently the preferred method due to its accuracy and reliability [21].

7. Epidemiology

Globally, gonorrhea is the second most common sexually transmitted infection, affecting 82.4 millions of individuals in 2020 alone. The highest incidence rates are observed in people aged 15-49 years, particularly in populations at higher risk for gonococcal infection. With the WHO African Region having the highest incidence rate, followed by the South-East Asia region [4]. While low- and middle-income countries tend to have higher prevalence rates, developed nations also face significant challenges in controlling the spread of the infection [22]. In fact, the incidence of reported cases of gonorrhea has been increasing in the European Union and the United States, with a 111% increase observed over 11 years in the latter. In 2019 and 2020, the number of cases per

100,000 people in the US increased from 187.8 to 206.5, respectively [23].

The prevalence of gonorrhea in Ethiopia is not consistent and varies depending on the population and region studied. Various studies have reported different rates of prevalence. For instance, a study conducted in Addis Ababa found that the prevalence of gonorrhea among the youth was 4.3% [24]. Another study conducted in Gambella hospital reported a prevalence of 11.3% among patients suspected to have STIs [25]. In Hawassa referral hospital, a study reported a prevalence of 5.1% among women experiencing symptoms attending gynecology outpatient department [26].

8. The Challenges of Drug-Resistant Gonorrhea

In recent years, *N.gonorrhoeae* has become resistant to multiple classes of antibiotics, including sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and third-generation cephalosporins [27].

Multi-drug resistant (MDR) *N. gonorrhoeae* refers to infections that are resistant to one antibiotic in category I (which includes injectable and oral extended-spectrum cephalosporins and spectinomycin) and at least two antibiotics in category II (which includes penicillins, fluoroquinolones, azithromycin, aminoglycosides, and carbapenems). Extensively drug-resistant (XDR) *N. gonorrhoeae,* on the other hand, is characterized by resistance to two or more antibiotics in category I and three or more in category II [28].

Sulfonamides were among the earliest antibiotics developed in the 1930s and were widely used for gonococcal therapy. However, their effectiveness declined rapidly after just ten years due to the emergence of resistance. The introduction of penicillin G in 1943 marked a significant breakthrough in antigonococcal treatment, with its effectiveness lasting for around 40 years. However, by the late 1980s, penicillin was no longer sufficient, and tetracycline (an alternative therapy) resistance also emerged [2]. In 1985, the Center for Disease Control (CDC) reported the appearance of tetracycline-resistant *N.gonorrhoeae* in three US states [29].

Fluoroquinolones were introduced in the late 1980s as a treatment for gonorrhea infections due to the widespread resistance to penicillins and tetracyclines [30]. However, by the early 1990s, the effectiveness of fluoroquinolones in Japan had rapidly declined.

By 1997, studies showed that approximately 10% of all gonococcal strains in Hong Kong and the Republic of the Philippines were resistant to fluoroquinolones [31]. In 2001, fluoroquinolone-resistant gonorrhea emerged in Hawaii and California, and by 2006, there was up to a 98.7% resistance rate to ciprofloxacin in Shanghai. Accordingly, once the resistance to fluoroquinolones reached 5% of the tested *N. gonorrhoeae* isolates in any region, it was recommended to switch to third-generation cephalosporins as the primary antibiotics for treating gonorrhea infections. Therefore, Ciprofloxacin was removed from guidelines in Asia, Europe, and the U.S. in the early to mid-2000s [32].

The first documented cases of clinical failure with oral cephalosporins in treating gonococcal urethritis were reported in Japan, followed by reports of resistance to third generation oral cephalosporins in several areas of Japan. As a result, cefixime was no longer used as the preferred treatment for gonorrhea in Japan starting in 2006. Treatment failures with cefixime have since been reported in multiple European countries, as well as Canada and South Africa [33]. The discovery of the highly ceftriaxone-resistant N. gonorrhoeae strain H041 in Japan caused global alarm as ceftriaxone is currently the only effective treatment option for empirical, first-line monotherapy of *N. gonorrhoeae.* Reports of ceftriaxone treatment failures in treating pharyngeal gonorrhea have been reported in several countries, including Japan, Sweden, Slovenia, and Australia. Moreover, the UK reported the first global treatment failure in late 2014 to a dual antimicrobial therapy regimen that includes ceftriaxone and azithromycin [27].

Numerous studies have been conducted to assess *N.gonorrhoeae's* resistance to antibiotics in Ethiopia. The latest study in Addis Ababa in 2022 found that natural penicillin and fluoroquinolone antibiotics were highly resistant, while cephalosporins, macrolides, and spectinomycin showed better susceptibility rates [34]. Similarly, studies from Jimma, Gondar, and Gambella had high instances of resistance to popular antibiotics like tetracycline, ciprofloxacin, and penicillin. However, ceftriaxone and spectinomycin were consistently effective in treating all isolates in these studies [25, 35, 36].

In 2014, a study from Addis Ababa provided insight into the antimicrobial susceptibility profile of *N.gonorrhoeae* that led to revisions of national syndromic guidelines. These findings reinforce the importance of updating treatment guidelines and regularly monitoring antibiotic resistance patterns to ensure effective management of gonorrhea in Ethiopia [37].

The challenges to develop new treatment

The WHO Global Gonococcal Antimicrobial Surveillance Programme was relaunched in 2009 to work with other national and regional gonococcal antimicrobial surveillance programs. These programs are critical in monitoring the trends, emergence, and spread of antimicrobial resistance in gonorrhea and in informing the development of the best empiric treatment recommendations. However, many regions, including the WHO Eastern Mediterranean Region, Eastern Europe, Central Asia, and Africa, lack effective gonococcal antimicrobial surveillance programs, gonorrhea rates are high and diagnostics and surveillance are suboptimal. Easy access to antimicrobials without prescription further compounds the problem, creating conditions for rapid emergence and spread of antimicrobial resistance [39].

Another significant challenge of drug resistance in *N. gonorrhoeae* is the lack of research on alternative treatments.

The pharmaceutical industry has historically shown little interest in developing new drugs to treat gonorrhoea. Treatments are taken only for short periods of time (unlike medicines for chronic diseases) and they become less effective as resistance develops, meaning that the supply of new drugs constantly needs to be replenished [40].

Moreover, the challenge is further exacerbated as most bacteria will lose antibiotic resistance once the antibiotic selective pressure disappears (when the drug is phased out of usage), *N. gonorrhoeae* retains resistant properties even after prolonged absence of the antibiotic Therefore, antibiotics that were once effective but discontinued decades ago cannot be re-introduced into the portfolio of treatments, as they can be for other pathogens that develop resistance. Not only does *N. gonorrhoeae* develop resistance quickly, but it also appears to be permanent in some cases [2].

Extra genital infections like anorectal and pharyngeal infections are more prevalent among key populations such as men who have sex with men. These infections are difficult to diagnose and treat, especially if they remain asymptomatic. Moreover, the interaction and exchange of genetic material between co-infections in these anatomical sites can contribute to the development of drug-resistant strains. This is because genetic exchange can lead to the acquisition of genetic mutations that confer antibiotic resistance. Therefore, the emergence of extra genital infections and the co-infections that result can greatly hinder efforts to control the spread of drug-resistant gonorrhea [41].

Why is this concerning? Because today, there is only one recommended treatment left for gonorrhea, and resistance to this regimen is emerging. If the number of gonorrhea cases continues to rise and no new treatments become available, it has the potential to become a serious epidemic.

The challenges to Health and Economic

Gonococcal infections can have serious consequences for reproductive, maternal and newborn health. These include a 5 fold increased risk of HIV transmission, as well as infertility, which can have social and cultural ramifications. In women, inflammation caused by the infection can result in acute and chronic lower abdominal pain, and can also lead to ectopic pregnancy, maternal death, and first trimester abortion. Additionally, severe neonatal eye infections caused by gonorrhea can result in blindness [41].

It is more cost-effective to prevent an epidemic rather than containing and eliminating one. The United States currently spends $162 million annually on gonorrhea, which could increase without prevention and control measures. Antibiotic-resistant gonorrhea could result in 1 million new gonorrhea infections and 600 new HIV infections over the next decade, costing $378.2 million in medical expenses. It is crucial to have resources focused on monitoring and responding to outbreaks of this type [42].

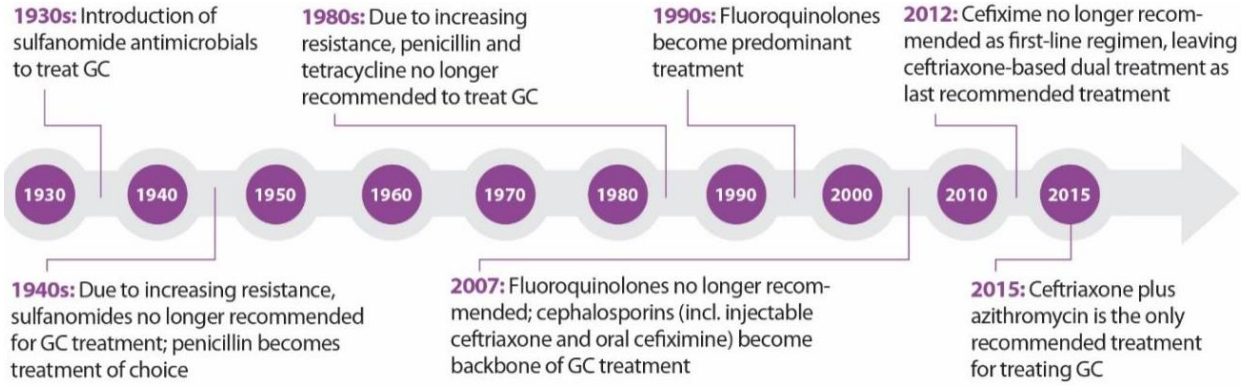

Figure 2. *Historical Trends in Drug Resistance and CDC Treatment Recommendations [38].*

9. Prospects for the Development of New Treatments and Vaccines

Several new drugs are currently being developed to target *N. gonorrhoeae,* some of the promising drug candidates include Zoliflodacin is a novel antibiotic that targets the GyrB subunit in DNA gyrase and is effective against ciprofloxacin-resistant strains of *N. gonorrhoeae.* It has shown promising results in both in vitro studies and clinical trials, with lower MICs than previously used antibiotics. A Phase II clinical trial showed high treatment success rates for urogenital and rectal gonorrhea, and while efficacy was lower for pharyngeal gonorrhea, zoliflodacin was still effective in most cases. Solithromycin is a fourth-generation macrolide that showed superior antibiotic activity to currently used antibiotics in in vitro studies and 100% efficacy in Phase II clinical trials [43]. However, a Phase III clinical trial comparing solithromycin to ceftriaxone and azithromycin dual therapy for uncomplicated genital gonorrhea failed to show non-inferiority and had a higher frequency of adverse events. Further evaluation is required for both zoliflodacin and solithromycin as potential alternative first-line treatments for *N. gonorrhoeae* [43, 44].

Developing a vaccine against *N. gonorrhoeae* has been

challenging due to the presence of antigenic variation in the pathogen. However, recent advancements in vaccine technology offer hope for the development of an effective vaccine. A number of stably expressed conserved antigens might be promising gonococcal vaccine targets. The main vaccine approaches include meningococcal outer membrane vesicle (OMV) vaccines, gonococcal OMV vaccines, a lipooligosaccharide epitope vaccine, and purified protein subunit vaccines [45]. Bacterial OMV vaccines, which contain various bacterial surface proteins, have shown promising results in preclinical studies and are safe and well-tolerated in Phase I clinical trials [46].

10. Conclusion

This comprehensive review on multidrug resistance gonorrhoeae, sheds light on various critical aspects, including its epidemiology, transmission, pathogenesis, clinical presentation, laboratory diagnosis, challenges of drug-resistant gonorrhea, health and economic implications, as well as prospects for the development of new treatments and vaccines. The escalating trend of AMR in N. gonorrhoeae poses a significant challenge to public health globally. The emergence of multidrug-resistant and extensively drug-resistant strains has severely limited treatment options, leading to prolonged infections, increased risk of complications, and higher transmission rates. This underscores the urgent need for intensified research, surveillance, and innovative strategies to combat this growing threat. Moreover, effective laboratory diagnosis, considering the limitations of conventional methods like culture and Gram stain, particularly in asymptomatic cases is crucial. NAATs emerge as a highly sensitive and specific tool for diagnosing gonorrhea, although challenges such as false positives due to cross-reaction with other Neisseria species remain.

Abbreviations

AMR: Antimicrobial Resistance
CDC: Center for Disease Control
DGI: Disseminated Gonococcal Infection
ESBLs: Extended-Spectrum Lactamases
XDR: Extensively Drug-Resistant
LOS: Lipooligosaccharide
MSM: Men Who Have Sex with Men
MIC: Minimum Inhibitory Concentration
MDR: Multi-Drug Resistant
NGU: Non-Gonococcal Urethritis
NAATs: Nucleic Acid Amplification Tests
Opa: Opacity-Associated
OMV: Outer Membrane Vesicle
PID: Pelvic Inflammatory Disease
PBPs: Penicillin-Binding Proteins
RDTs: Rapid Diagnostic Tests
Rmp: Reduction-Modifiable Proteins
STIs: Sexually Transmitted Infections
WHO: World Health Organization

Conflicts of Interest

The authors declare no conflicts of interest.

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