Journal of Health and Medical Sciences

Dewi, D. A. R., Arkania, N., Wiliantari, N. M., Nadhira, F., Allun, C. V., Allatib, A., Salsabila, C. A., Dewantara, K., & Perdiyana, A. (2023), Alternative Antibiotics Therapy for Drug-resistant Gonorrhea: A Literature Review. *Journal of Health and Medical Sciences*, 6(3), 32-51.

ISSN 2622-7258

DOI: 10.31014/aior.1994.06.03.275

The online version of this article can be found at:
https://www.asianinstituteofresearch.org/

Published by:
The Asian Institute of Research

The Asian Institute of Research *Journal of Health and Medical Sciences* is a peer-reviewed International Journal. The journal covers scholarly articles in the fields of Medicine and Public Health, including medicine, surgery, ophthalmology, gynecology and obstetrics, psychiatry, anesthesia, pediatrics, orthopedics, microbiology, pathology and laboratory medicine, medical education, research methodology, forensic medicine, medical ethics, community medicine, public health, community health, behavioral health, health policy, health service, health education, health economics, medical ethics, health protection, environmental health, and equity in health. As the journal is Open Access, it ensures high visibility and the increase of citations for all research articles published. The *Journal of Health and Medical Sciences* aims to facilitate scholarly work on recent theoretical and practical aspects of Health and Medical Sciences.

ASIAN INSTITUTE OF RESEARCH
Connecting Scholars Worldwide

The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.6, No.3, 2023: 32-51
ISSN 2622-7258

DOI: 10.31014/aior.1994.06.03.275

Alternative Antibiotics Therapy for Drug-resistant Gonorrhea: A Literature Review

Dian Andriani Ratna Dewi[1], Nabila Arkania[2], Ni Made Wiliantari[3], Farrasila Nadhira[4], Clara Virginia Allun[5], Arohid Allatib[6], Cut Annisa Salsabila[7], Kelvin Dewantara[8], Angki Perdiyana[9]

[1,5,6,7,8,9] The Republic of Indonesia Defense University. Email: dianandrianiratnadewi@gmail.com
[2] Central General Hospital Dr. Sardjito Yogyakarta, Indonesia
[3] Ratna Dewi Principal Clinic, Indonesia

Correspondence: Dian Andriani Ratna Dewi. Email: dianandrianiratnadewi@gmail.com

Abstract
Background: The management and control of gonorrhea are hampered by the widespread resistance to the diverse strains of *Neisseria gonorrhea*. Resistance to sulfonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early cephalosporins has emerged rapidly. Purpose: This systematic review aimed to assess what antibiotics can be used as an alternative therapy for gonorrhea infections that are resistant to antibiotics. Methods: The study was conducted using the Web of Science, PubMed, Embase, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines. Risk of Bias for Randomized Trials (RoB2) was utilized to evaluate study quality. Results: This review included 28 articles from randomized controlled trials between 2013 and 2023, distributed across five nations. The studies included 2.380 patients and clinical isolates from men and women diagnosed with gonorrhea infection at various sites. Sample testing by treatment with alternative antibiotics. Discussion: Zoliflodacin, tigecycline, and ertapenem in single or dual therapy with ceftriaxone could be considered as a potential option in treating gonorrhea resistant to antibiotics. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gepotidacin is effective for the Gyr A A92T mutation in gonorrhea infection. Summary: The effectiveness of these antibiotics, zoliflodacin, ceftriaxone, gentamicin, gepotidacin, solithromycin, tigecycline, and ertapenem is considered a solution to gonorrhea resistance. Researchers should study how to provide antibiotics with intervening multidrug efflux pumps to overcome gonococcal antimicrobial resistance.

Keywords: Gonorrhoea, Resistance Antibiotic, Alternative Antibiotics

1. Introduction

The prevalence of bacterial resistance to antibiotics is accountable for a significant number of fatalities annually, reaching hundreds of thousands. One of the most pressing issues pertains to the escalating prevalence of bacteria that have developed resistance against frequently employed antibiotics, particularly those considered the final line of defense. This requires international cooperation. In 2014, the World Health Organization (WHO) acknowledged this occurrence as a significant worldwide health concern (Shafran, 1990). In a recent development, the World

Health Organization (WHO) has identified antibiotic resistance as one of the foremost worldwide public health challenges confronting the human population. It is predicted that antibiotic-resistant infectious diseases will have a global impact, affecting a minimum of 700,000 individuals each year. Projections indicate that by the year 2050, these infections could be responsible for around 10 million fatalities a year and cause significant economic damage on a global scale (Coates et al., 2020).

The effective management and control of gonorrhoea are impeded by the extensive resistance exhibited by the varied strains of *Neisseria gonorrhoeae*. The emergence of resistance to sulfonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early cephalosporins has occurred at a rapid pace. In the present context, it is widely acknowledged that ceftriaxone stands as the sole empirical monotherapy for the treatment of gonorrhoea in the majority of nations. Antimicrobial resistance is a multidimensional and intricate issue that is influenced by a range of circumstances (Uddin et al., 2021):

a. The augmentation of bacterial population density within healthcare facilities facilitates the transmission of bacteria to the wider community.
b. The hospital's failure to comply with hygiene procedures and regulations aimed at maintaining cleanliness contributes to the escalation of antimicrobial resistance (AMR) in bacteria.
c. The overutilization of antibiotics in the agricultural sector.
d. International travel and trade can potentially lead to the dissemination of germs that are resistant to dispersion.
e. In certain regions, there is an insufficiency in sanitation practices, resulting in the potential contamination of water systems and the dissemination of antibiotic-resistant bacteria within sewage networks.
f. The excessive utilization of antibiotics in the field of human medicine, such as their application for the treatment of viral illnesses that are contagious in nature.
g. The absence of prompt diagnostic methods to facilitate the judicious administration of antibiotics is one of the key issues.

The degree of resistance expression, the microorganism's tolerance of resistance mechanisms, the place of initial colonization, and other host variables all play a role in the formation of an antimicrobial-resistant phenotype. When the factors that determine resistance are found on plasmids, they spread quickly within bacterial genera and sometimes even between different bacterial genera. Microorganisms with resistance that is connected to chromosomal genes will proliferate more slowly (Stratton, 2000). An important cause of the spread of antimicrobial resistance is the failure to implement infection control either in the hospital or outside the hospital (WHO, 2016).

The most basic form of resistance is characterized by a diminished natural vulnerability, sometimes referred to as innate resistance. The potential reasons for this occurrence may include the lack of receptors for antibiotics, reduced affinity, impermeability of the cell wall, or the synthesis of enzymes (Urban-Chmiel et al., 2022). Bacteria acquire partial or complete resistance to specific antibiotics through the development of diverse effector mechanisms, which are facilitated by the presence of resistance genes (Darby et al., 2023).

Numerous scientific investigations undertaken since the mid-20th century have elucidated several processes that account for bacterial resistance to antibiotics (Giedraitienė et al., 2011).

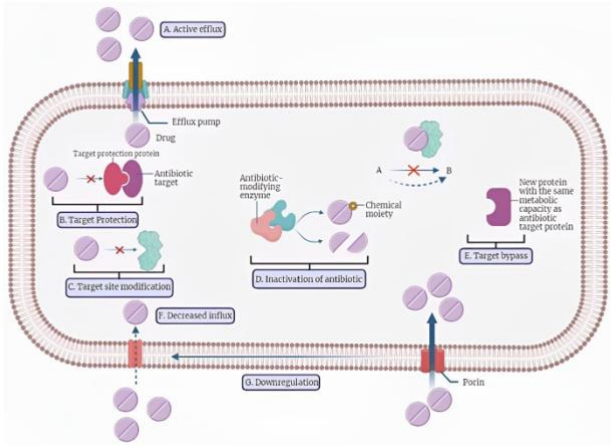


Figure 1: Molecular mechanisms of antibiotic resistance.

A. Active efflux is enabled through an efflux pump located on the transmembrane, which expels antibiotics from the bacterial cell, thereby diminishing their intracellular concentration (Masi & Pagès, 2013).
B. The target becomes protected due to the presence of a protein that protects the antibiotic target, so it is free from antibiotic-mediated inhibition (Doi et al., 2017).
C. Target bypass, the antibiotic target is actually occupied by a new protein that is not inhibited by the antibiotic, so the initial target does not work and the antibiotic is ineffective.
D. Changes in the target location result in changes in the antibiotic's target thereby reducing the binding of the antibiotic. This can occur due to gene mutations that code for protein targets of antibiotic or enzymatic molecules at binding sites (Lambert, 2005).
E. Antibiotics exert their effects by altering the activity of enzymes responsible for transferring diverse chemical groups onto the antibiotic molecule, thereby impeding the binding of the antibiotic to its intended target. Enzymatic degradation refers to the process of hydrolyzing the functional groups of the antibiotic, resulting in its loss of effectiveness (Varela et al., 2021).
F. The reduction in the rate of inflow is facilitated by alterations in the structure of the membrane, namely by the downregulation of porins. Porins are transmembrane proteins responsible for enabling the passive transport of substances into the bacterial cell (Masi & Pagès, 2013).

Based on the background above, we found a problem that we will discuss in this review. First is the pattern of evolution of *N. gonorrhoea*'s resistance to antibiotics: second, what antibiotics can be used as alternative therapies in cases of gonorrhea infections that are resistant to antibiotics.

2. Methods

2.1. Search strategies

The procedure utilized in this systematic review adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, which provides a standardized framework for reporting systematic reviews. A comprehensive literature review was undertaken using PubMed, Embase, Central, and Web of Science. Several keywords were used to find relevant studies: antibiotic-resistance, gonorrhea infection, and randomized controlled trials (RCTs). The initial search was conducted on July 30th, 2023. Inclusion criteria:

- The study that consists of alternative therapy for antibiotic-resistant gonorrhea infection
- The study with a randomized controlled trial study design
- Peer-reviewed article published between 2013-2023

Exclusion criteria:

- The study was a non-randomized controlled trial
- Observational article

- An article that only explains antibiotic resistance

2.2. Data extraction

The titles and abstracts were thoroughly examined to ensure their alignment with the predetermined inclusion criteria. The complete reports were subsequently evaluated to see whether the publications met the inclusion criteria, which encompassed outcomes, interventions, research designs, and patient demographics. The rationales for the exclusion of studies were elucidated.

2.3. Quality assessment

The methodological quality of the research was assessed by two independent reviewers (CVA and CAS) using the Risk of Bias 2 (RoB2) methods. Cochrane Reviews only comprise randomized studies that have undergone evaluation of their risk of bias utilizing the Cochrane risk-of-bias tool for randomized trials, version 2. The defined categories of bias in RoB 2 cover a wide variety of possible issues with trials and their reporting. The goal of a series of inquiries known as "signaling questions" is to obtain information regarding trial characteristics relevant to each domain's risk of bias. An algorithm proposes a bias risk estimate for each domain based on the replies to the signaling questions. Bias risk ratings can vary from "Low" to "High," with "Some concerns" as an option.

2.4. Description of selected studies

The systematic search showed 28 results. Only peer-reviewed English-language publications published between 2013 and 2023 were considered. The datasets underwent a process of removing a single instance of duplicated research. A total of 27 articles were assessed based on their titles and abstracts, resulting in the evaluation of 23 full-text papers. Seventeen studies were eliminated because they had the incorrect setting (n = 6), indication (n = 1), intervention (n = 1), research design (n = 6), and patient population (n = 3). Six studies were considered in this analysis. Please have a look at Figure 2 and Table 1.

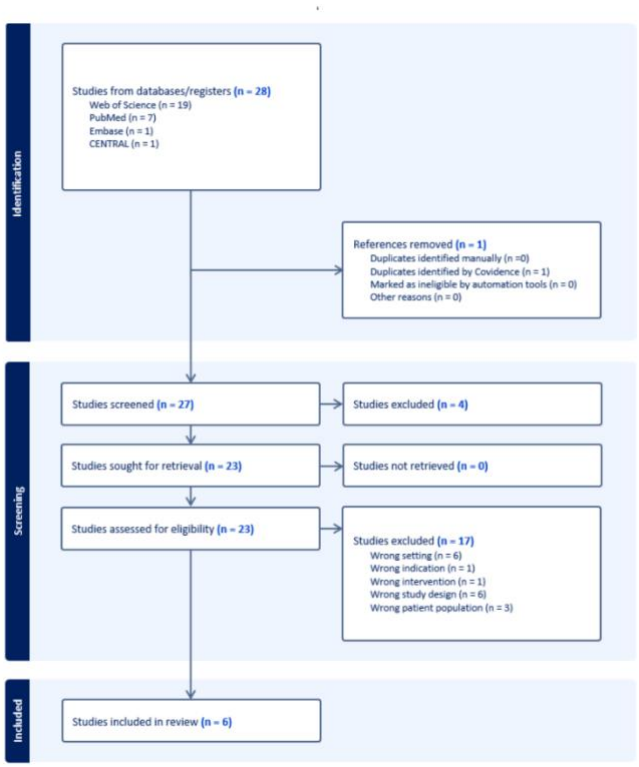
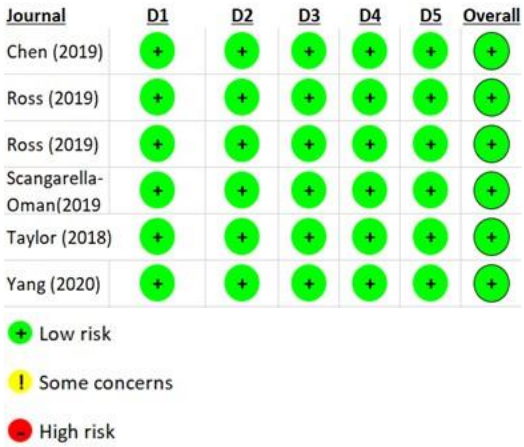


Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram



D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Table 1: Summary of Selected Study Characteristics

No.	Title	Author, year (Country)	Aim of study	Population and Intervention	Result and Outcomes
1.	Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea	(Taylor et al., 2018) (New Orleans)	Evaluated Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea	Total participants: 179 (167 men and 12 women) men and nonpregnant women aged 18 to 55 years urogenital gonorrhea without complication sexual contact within the past 14 days with a person diagnosed with gonorrhea.	141 participants were eligible for evaluation. Result: urogenital infections were successfully cured in a high percentage 2 g of zoliflodacin, 96% (55 out of 57 participants) 3 g of zoliflodacin (96%, 54 out of 56 participants) and ceftriaxone (100%, 28 out of 28 participants). For rectal infections: 2 g of zoliflodacin(5 participants) 3 g of zoliflodacin (7 participants) ceftriaxone group (3 participants. 21 adverse events as being related to zoliflodacin, most of these: gastrointestinal in nature.
2.	Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial	(Ross, Brittain, et al., 2019) (London)	Tho assess whether single-dose gentamicin therapy is an acceptable alternative to ceftriaxone for the treatment of gonorrhea when both antibiotics are combined with azithromycin	720 were enrolled (362 were assigned to receive ceftriaxone and 358 to receive gentamicin) 322 (89%) of 362 participants allocated to ceftriaxone and 302 (84%) of 358 participants allocated gentamicin	The median time from randomization to follow-up was 16 days (IQR 14-20) in the ceftriaxone group and 15 days (IQR 14-20) in the gentamicin group. 267 (83%) of 322 participants in the ceftriaxone group and 248 (82%) of 302 participants in the gentamicin group returned within 21 days. 2 weeks after treatment, the infection had cleared for 299 (98%) of 306 participants allocated to ceftriaxone compared with 267 (91%) of 292 participants allocated to gentamicin (adjusted risk difference -6·4%, 95% CI -10·4% to -2·4%. Gentamicin plus azithromycin cannot be considered non-inferior to ceftriaxone plus azithromycin, with a relatively higher frequency of treatment failure extragenital gonorrhoea who were treated with gentamicin. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gentamicin combined with 1 g azithromycin achieved a cure rate of 94% for genital gonorrhoea might be appropriate in patients who are allergic, intolerant, or harbour a ceftriaxone-resistant infection.
3.	Microbiological analysis from a	(Scangarella-Oman et al.,	Evaluated microbiological	The microbiologically	The success rate was 100% (61/61) when the fAUC/MICs (free drug area under the

	phase 2 randomized study in adults evaluating single oral doses of gepotidacin in the treatment of uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae*	2018) (Alabama, USA)	correlates for the successful treatment of *N. gonorrhoeae* isolates from a phase 2 study of gepotidacin, a novel triazaacenaphthylene antibacterial, for therapy of uncomplicated urogenital gonorrhea.	evaluable population consisted of 69 randomly assigned participants (67 male and 2 female) with culture-confirmed urogenital gonorrhea at baseline who received gepotidacin and returned for TOC. Culture, susceptibility testing, genotypic characterization, and frequency of resistance (FoR) were performed for selected isolates.	concentration-time curve to minimum inhibitory concentration ratio) were at 48, but it decreased to 63% (5/8) when the fAUC/MICs were at 25. 3 were resistant to ciprofloxacin, carried a preexisting ParC D86N mutation. In a test-of-cure analysis, resistance to gepotidacin emerged in two with additional GyrA A92T mutations. For five selected baseline isolates, all carrying the ParC D86N mutation, the in vitro FoR (frequency of resistance) to gepotidacin was low (ranging from 10^9 to 10^10); In conclusion, fAUC/MICs of 48 were associated with 100% microbiological success, even including three isolates with the ParC D86N mutation (fAUC/MICs ≥ 97).
4.	Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: The G-TOG non-inferiority RCT	(Ross, Harding, et al., 2019) (UK)	To provide information on the safety, effectiveness, and cost-effectiveness of gentamicin compared to ceftriaxone for the treatment of gonorrhoea.	Gentamicin compared to ceftriaxone for the treatment of gonorrhoea. It was estimated that a total sample size of 646 participants for analysis (323 in each group) would achieve 90% power at the 2.5% one-sided significance level to detect non-inferiority with a lower 95% confidence interval (CI) for the absolute risk difference of 5%.	1. Primary Outcome: The clearance rate of *N. gonorrhoeae* infection at the pharynx, rectum, and urethra was similar between the gentamicin and ceftriaxone groups. 2. Secondary Outcomes: - Clinical resolution of symptoms: Both gentamicin and ceftriaxone groups showed similar rates at 2 weeks post-treatment. The cost-effectiveness of gentamicin compared to ceftriaxone was evaluated using a decision tree model. The results showed that gentamicin was cost-effective compared to ceftriaxone for the treatment of gonorrhea.
5.	Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial	(Chen et al., 2019) (Australia and USA)	To compare the efficacy and safety of solithromycin with ceftriaxone plus azithromycin for the treatment of gonorrhea.	(1) Total of 262 patients, with 131 : solithromycin group 131 : cefriaxone plus azithromycin group. (2) The majority of patients were men (94%), particularly men who have sex with men (72%). (3) Mean age: 30.1 years in the solithromycin group and 29.4 years in the ceftriaxone plus azithromycin group. (4) Some patients had co-infections with chlamydia at various anatomical sites.	The primary outcome: eradication of genital gonorrhea based on culture at day 7. 80% of patients in the solithromycin group and 84% of patients in the ceftriaxone plus azithromycin group Secondary outcomes: proportion of patients with eradication of gonorrhea based on culture at day 7 at each anatomical site, clearance of gonorrhea based on NAAT at day 7, and clearance of chlamydia based on NAAT at day 21. The study found that solithromycin was non-inferior to ceftriaxone plus azithromycin in achieving these secondary outcomes. Adverse events were similar between the two treatment groups, with gastrointestinal events being the most common.
6.	Evaluation of alternative antibiotics for susceptibility of gonococcal isolates from China (2019)	(Yang et al., 2020) (China)	To evaluate the susceptibility of *N. gonorrhoeae* isolates from China to alternative antibiotics	The population in this study consisted 504 clinical isolates of *N. gonorrhoeae* obtained from seven hospitals in Zhejiang province, China The intervention in this study involved evaluating the susceptibility of these isolates to alternative antibiotics	Among the 504 clinical isolates there was a high prevalence of decreased susceptibility to ceftriaxone and resistance to azithromycin. Tigecycline and ertapenem showed potential as alternative antimicrobials for the treatment of gonorrhea. Tigecycline and ertapenem could be considered as potential options for single or dual therapies, possibly in combination with ceftriaxone. Need for further research and clinical trials to evaluate the efficacy of these alternative antibiotics in the management of gonorrhea.

3. Discussion

3.1. Evolution of Antimicrobial Resistance

The bacterium *Neisseria gonorrhoeae* has exhibited the emergence of resistance to antibiotic treatment. The rise of strains that are resistant to ceftriaxone poses a significant threat to the limited remaining therapeutic options available. The development of the Gonococcal Resistance to Antimicrobials Surveillance Programme Action Plan (GRASP) in 2013 aimed to mitigate the proliferation of antimicrobial resistance (AMR) in England. The period spanning from 2013 to 2019 witnessed a substantial increase in the incidence of gonorrhoea cases in the United Kingdom, with a surge of 128% resulting in a record-breaking annual figure of 70,922 diagnoses (Lawrence et al., 1973). Antimicrobial resistance to sulfonamide, macrolides (including azithromycin), penicillin, tetracylin, quinolones, and even ceftriaxone as a first line therapy has been documented in a significant proportion of the gonococcal population with depressing regularity over extended periods. In the worst-case scenario, gonorrhea may become untreatable (Tapsall et al., 2009). (Figure 3)

3.2. Sulfonamides

The utilization of sulfonamides as a therapeutic intervention for the treatment of gonorrhoea was first introduced in the 1930s. Nevertheless, it was documented that in 1944, a significant proportion of World War II soldiers engaged in the Italian and Sicilian campaigns saw a treatment failure rate of 75% when administered with sulfathiazole or sulfapyridine (Campbell & Ed, 1944).

During the 1960s, a proposal was made to enhance the effectiveness of sulfonamide in the treatment of simple gonorrhoea by implementing a combined therapy involving trimethoprim. Until the 1970s, the therapeutic approach for treating gonorrhoea was the utilization of sulfonamides in conjunction with trimethoprim, which was found to exhibit a synergistic effect. This treatment regimen involved the administration of high doses of the combined drugs at many intervals (Lawrence et al., 1973).

3.3. Penicillin

The utilization of penicillin as an antibacterial therapy for gonorrhoea commenced in 1943. Nevertheless, the effectiveness of penicillin against gonococcus began to decline in the 1960s. Penicillin, functioning as a β-lactam antimicrobial agent, exerts its inhibitory effect on the formation of bacterial cell walls by specifically binding to transpeptidase enzymes known as penicillin-binding proteins (PBP) located in the periplasmic space. In the initial five decades of penicillin utilization, the development of resistance mechanisms in the gonococcus bacterium was observed to be associated with a decline in susceptibility. This decline was attributed to the accumulation of chromosomal mutations in various genes involved in the biosynthesis of the cell wall (penA and ponA1), as well as structures that impact the concentration of drugs in the periplasmic space (penB, penC, and mtrR) (Lobanovska & Pilla, 2017).

3.4. Tetracycline

The introduction of tetracycline in the 1950s provided an alternative treatment for people with gonorrhoea who exhibited allergic reactions to penicillin. The protein synthesis process is impacted by the antimicrobial agent through its interaction with the 30S ribosomal subunit. Just as with the development of resistance to penicillin, resistance to tetracycline emerged gradually over time. Indeed, certain chromosomal changes associated with resistance to penicillin, such as penB and mtr overexpression, have been found to hinder the effectiveness of tetracycline (Unemo & Shafer, 2014).

The initial identification of gonococcus isolates exhibiting high-level resistance to tetracycline was seen in the United States in 1985. The mechanism underlying the resistance phenotype, which shields the ribosome from tetracycline binding, has been elucidated with the identification of the TetM protein. The emergence of resistance

in the treatment of gonorrhoea during the quinolone period can be traced back to the discontinuation of tetracycline as a suggested therapeutic option in the mid-1980s (Costa-Lourenço et al., 2017).

3.5. The quinolone era in gonorrhea treatment

The development of ciprofloxacin occurred in 1983. In the early stages, the treatment of gonorrhoea involved the administration of ciprofloxacin in a single dose of 250 mg. Nevertheless, due to initial reports of reduced effectiveness, the initial recommendation from the Centers for Disease Control and Prevention (CDC) for ciprofloxacin treatment of this sexually transmitted infection (STI) was a single dose of 500 mg (Unemo & Shafer, 2014).

Quinolones exert their influence on DNA gyrase and topoisomerase IV, two crucial topoisomerases involved in several cellular processes such as DNA replication, transcription, recombination, and repair. This category of antimicrobial medicines functions by creating a complex including the drug, enzyme, and DNA, resulting in the release of double-strand DNA breaks. The resistance of *N. gonorrhoeae* to ciprofloxacin is facilitated by genetic changes occurring in the quinolone resistance-determining region (QRDR), which is situated in close proximity to the DNA binding site of the topoisomerases. These alterations collectively impact the susceptibility of isolates. Mutations resulting in a singular alteration of a single amino acid at positions 91 or 95 in the GyrA protein are associated with an intermediate level of resistance. However, when three or more amino acid changes occur at positions 91, 95, and 102 in the GyrA protein, as well as at positions 87 and 91 in the ParC protein and position 439 in the ParE protein, higher levels of resistance are observed (Hooper & Jacoby, 2016).

Ciprofloxacin treatment, which was first recommended as the primary treatment for gonorrhoea in the United States, was discontinued in the Asian Western Pacific region due to the emergence of significantly elevated resistance rates. In the context of Japan, it is noteworthy that the rate of resistance stood at 6% during the period of 1993–1994, and then experienced a significant increase to 24% in the years 1997–1998 (Costa-Lourenço et al., 2017).

3.6. Azithromycin

The inclusion of azithromycin as a potential therapeutic option for the treatment of gonorrhoea began in the early 1980s. This particular macrolide compound exhibits an interaction with the P site of the 50S ribosomal subunit, resulting in the inhibition of the peptidyl transferase activity and subsequent impairment of the elongation process of the polypeptide chain (Zarantonelli et al., 1999).

One of the factors contributing to the increased resistance of *N. gonorrhoeae* to penicillin and enhanced sensitivity to azithromycin is the upregulation of the efflux pump mtrCDE. This upregulation is mediated by the same molecular pathways previously described to reduce susceptibility to penicillin. Another way in which azithromycin decreased susceptibility might emerge is through the presence of mutations in the L4 ribosomal protein. The protein in question exhibits close proximity to the peptidyl-transferase area located inside the V domain of the 23S rRNA. Mutations that result in significant alterations to the amino acid sequence, such as the G70D mutation observed in its extended loop, have the potential to indirectly influence the conformation of the rRNA. In recent years, there has been an emergence of *N. gonorrhoeae* strains that demonstrate a significant degree of resistance to azithromycin. The initial instance transpired in Argentina during the year 2001 (Zarantonelli et al., 1999).

3.7. Ceftriaxone

The extended-spectrum cephalosporin ceftriaxone exhibits significant efficacy against gram-negative bacteria, particularly *N. gonorrhoeae*, through its strong binding affinity to penicillin-binding protein 2 (PBP2). The utilization of ceftriaxone as a standalone treatment for gonococcal infections emerged in response to the increasing prevalence of ciprofloxacin resistance. Cefixime, an oral extended-spectrum cephalosporin (ESC), was employed prior to the introduction of ceftriaxone. Nonetheless, the efficacy of this antibacterial agent diminished rapidly (Fenton et al., 2021).

The development of resistance to extended-spectrum cephalosporins (ESC) may be facilitated by genetic modifications in the penB, mtrR, and penC genes. However, it is primarily mutations in the penA gene, responsible for encoding penicillin-binding protein 2 (PBP2), that appear to be the primary determinant of ceftriaxone resistance. The modified penA gene can arise due to point mutations or by genetic recombination between commensal *Neisseria spp*. that inhabit different human sites, leading to the formation of a mosaic-like structure. The modified penicillin-binding protein 2 (PBP2) exhibits reduced binding affinity towards ceftriaxone (Fenton et al., 2021).

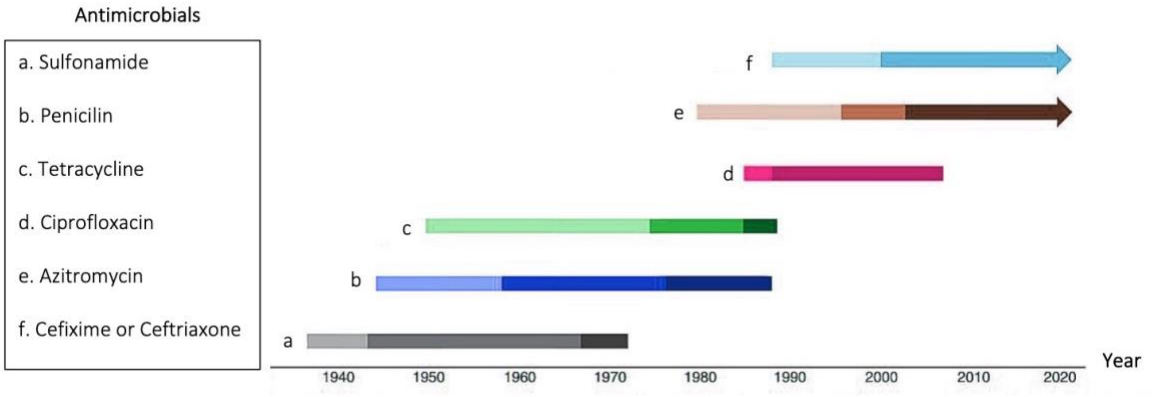


Figure 3: The phenomenon of antibiotic resistance in *Neisseria gonorrhoeae*. The color changer serves as an indicator of events that have negatively impacted the efficacy of antimicrobial agents over time, leading to a decrease in their resistance levels. Sulfonamide: an introduction, incidence of resistance, co-administration with trimethoprim: penicillin and tetracycline: an introduction, chromosomally-mediated resistance, plasmid-mediated resistance: ciprofloxacin: an introduction, reported resistance: azithromycin: an introduction, reported resistance, high-level resistance: cefixime or ceftriaxone: an introduction, reduced susceptibility reported.

4. Various Effective Therapeutic Antibiotics are used to Overcome Resistance in Gonorrhea

The development of alternative antimicrobial therapy is urgently needed to ensure that gonorrhea treatment remains available in the future. From various studies aimed at treating gonorrhea that is resistant to antibiotics, the effectiveness of these antibiotics is considered to be a solution to gonorrhea resistance. These antibiotics are zoliflodacin, ceftriaxone, gentamicin, gepotidacine, solithromycin, tigecycline, and ertapenem.

4.1. Gentamicin

In recent years, gentamicin has emerged as a prominent alternative antimicrobial agent for combating resistant gonorrhea. Extensive research efforts have been dedicated to investigating the efficacy of gentamicin in various clinical trials, both as a component of dual therapy and, more recently, as a standalone treatment option. Gentamicin is an aminoglycoside antibiotic that binds to 30S ribosomal subunits in an irreversible manner to prevent protein synthesis (Ross, Brittain, et al., 2019). The utilization of this treatment has been observed in numerous developing nations for the management of gonorrhoea, offering the distinct advantage of exhibiting both notable therapeutic efficiency and cost-effectiveness (Liu et al., 2019). The gonorrhea-causing bacterium *Neisseria gonorrhoeae* is inhibited from synthesizing proteins by the aminoglycoside drug gentamicin. To accomplish this, it binds to the decoding location where the 30S ribosomal subunit of bacteria is located, disrupting protein synthesis and causing bacterial death. It has been demonstrated that gentamicin can successfully treat gonorrhea, especially when combined with other antibiotics such as azithromycin or ceftriaxone. The development of medication resistance may be slowed down with the use of this combination therapy (Xu et al., 2022). (Figure 4)

In areas with limited resources, gentamicin is an affordable antibiotic used to treat genital gonorrhoea infections. Studies conducted in Malawi reveal that gonococcal isolates are very susceptible to gentamicin, with 95% clinical cure rates when coupled with doxycycline (Hathorn et al., 2014). Gentamicin has been proposed as an alternative

treatment option to ceftriaxone in guidelines issued by the American, European, and World Health Organization (WHO). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) do not provide any established criteria for determining the resistance of *Neisseria gonorrhoeae* to gentamicin. A point mutation in the fusA gene, responsible for encoding the elongation factor G (EF-G), results in a missense mutation that leads to an A563V substitution specifically in the IV domain of EF-G. The alternative form of the gene, known as fusA2, was designated as the mutant allele (Mlynarczyk-Bonikowska et al., 2022). In a study conducted by Holley et al., it was demonstrated that fusA2 has the ability to elevate the minimum inhibitory concentration (MIC) of gentamicin by a factor of four, resulting in a MIC value of 32 mg/L. While the presence of fusA2 did not hinder the development or protein synthesis of gonococci in vitro, it did result in a decrease in fitness when the lower vaginal tract of female mice was experimentally infected (Holley et al., 2022).

According to Ross et al, 2019, it is not suggested to substitute ceftriaxone with gentamicin as the first-line therapy for gonorrhoea. Nonetheless, the combination of gentamicin and 1 g azithromycin demonstrated a cure rate of 94% for genital gonorrhoea. This treatment option could be considered suitable for people who exhibit allergies, intolerances, or are afflicted with a ceftriaxone-resistant illness (Ross, Brittain, et al., 2019).

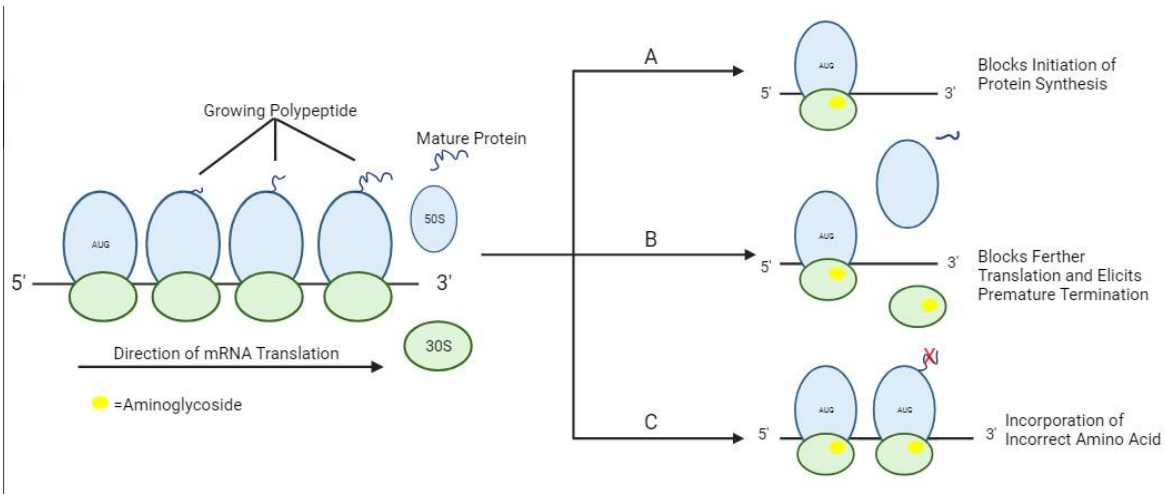


Figure 4: Impact of aminoglycosides on the process of protein synthesis. A. Aminoglycosides, shown as red circles. This interaction disrupts the initiation phase of protein synthesis by stabilizing the 30S–50S ribosomal complex at the mRNA start codon (AUG). Accumulation of aberrant initiation complexes inhibits the continuation of mRNA translation downstream. Binding of aminoglycosides to the 30S ribosomal subunit has been observed to induce the phenomenon of mRNA misreading, resulting in B. Premature end of translation, characterized by dissociation of the ribosome complex and production of a completely unsynthesized protein C. Insertion of the wrong amino acid (denoted by a red X) causes synthesis anomalous or dysfunctional proteins.

4.2. Ceftriaxone

The increasing prevalence of gonococcal resistance to non-cephalosporin categories of antimicrobial drugs has necessitated the utilization of cephalosporins, namely the administration of ceftriaxone via intramuscular injections and cefixime orally. However, trends in increasing mean minimum inhibitory concentrations (MICs) of *N. gonorrhoeae* for both agents, indicating decreasing susceptibility, have been reported worldwide and have led to changes in the recommendations for use of these agents. Research conducted by Ross et al., 2019 shows that the clearance rate of *Neisseria gonorrhoeae* infection at the pharynx, rectum, and urethra was similar between the gentamicin and ceftriaxone groups. Ceftriaxone is a pharmacologically potent bactericidal agent that functions by interfering with the process of bacterial cell wall synthesis, hence playing a crucial role in efficiently combating a wide range of diseases. By specifically binding to penicillin-binding proteins, it has the ability to thwart the activities of penicillinase and cephalosporins, which ensures its efficacy against both Gram-negative and Gram-positive bacterial strains. When administered, ceftriaxone attaches itself to the penicillin-binding proteins present in bacterial cells, thereby impeding the final transpeptidoglycan step crucial for peptidoglycan synthesis in the cell

wall. This crucial interruption leads to the inhibition of cell wall assembly and, consequently, the death of bacterial cells (Bereda, 2022). (Figure 5)

Ceftriaxone, a potent third-generation cephalosporin with extended-spectrum activity, boasts an impressive cure rate ranging from 72% to 97% and demonstrates exceptional efficacy against both gram-negative and gram-positive bacteria. This antimicrobial agent has been widely used in healthcare facilities over the last two decades, often prescribed for empirical treatment to address diverse infections. A quarter-century-old study sought to investigate the incidence of bacterial species and their responses to ceftriaxone and other lactam antibiotics in people with community-acquired illnesses (Tewabe et al., 2021).

In gonococci, β-lactam antibiotics encounter resistance through rapid plasmid-mediated β-lactamase production and gradual chromosomal gene mutations. Ceftriaxone resistance is linked to extended-spectrum β-lactamase production in E. coli and the presence of specific β-lactamases in Salmonella isolates. These mechanisms play a significant role in the spread of cephalosporin resistance, particularly ceftriaxone (Tewabe et al., 2021).

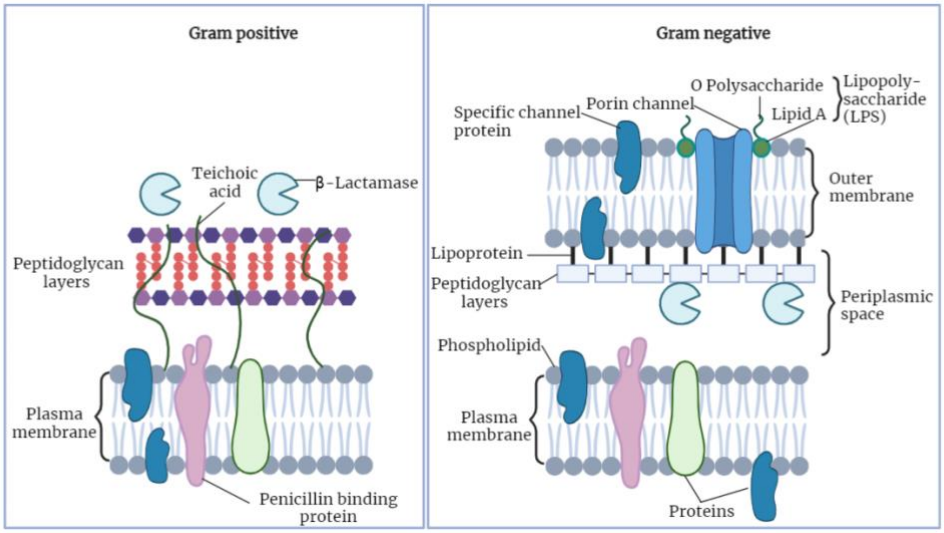


Figure 5: Structure and composition of gram-positive and gram-negative cell walls. Ceftriaxone acts as a transpeptidase enzyme that inhibits the transpeptidation reaction and then inhibits the synthesis of peptidoglysin. Activation of the autolytic enzymes causes an increase in cell membrane permeability, resulting in cell bursting and lysis.

4.3. Gepotidacin

In early clinical trials, gepotidacin, a novel antibiotic, has shown promising results for the treatment of urinary tract infections (UTIs), urogenital gonorrhea. It was developed in response to the rising bacterial resistance to fluoroquinolone drugs such as ciprofloxacin. This is a type of antibiotic known as triazaacenaphthylene, and how it works like fluoroquinolones is to stop bacterial DNA replication by stopping two important topoisomerase enzymes, DNA gyrase and DNA topoisomerase IV. The presence of these enzymes is crucial for the processes of DNA repair and replication in bacteria, and they are responsible for unwinding and resealing DNA strands during replication, which ensures the proper separation and organization of the DNA. It is unclear how gepotidacin resistance manifests in gonorrhea. The target enzymes gepotidacin, DNA gyrase and DNA topoisomerase IV, are thought to be susceptible to changes that might lead to treatment resistance. Gepotidacin's ability to limit DNA replication by diminishing its binding affinity to the target enzymes has been demonstrated in studies to be diminished by mutations in these genes, which can also result in resistance (Ross, Brittain, et al., 2019). (Figure 6)

The quinolone resistance-determining regions (QRDRs), which are recognized hotspots for resistance mutations in quinolone antibiotics, are one such area of the genes where these mutations might arise. Given that gepotidacin

is still in its early phases of development and clinical trials, it is significant to highlight that resistance to the medicine is not yet pervasive in gonorrhea. However, to guarantee the long-term efficacy of gepotidacin against gonorrhea, ongoing monitoring of resistance patterns and observation of infection trends will be essential (Unemo

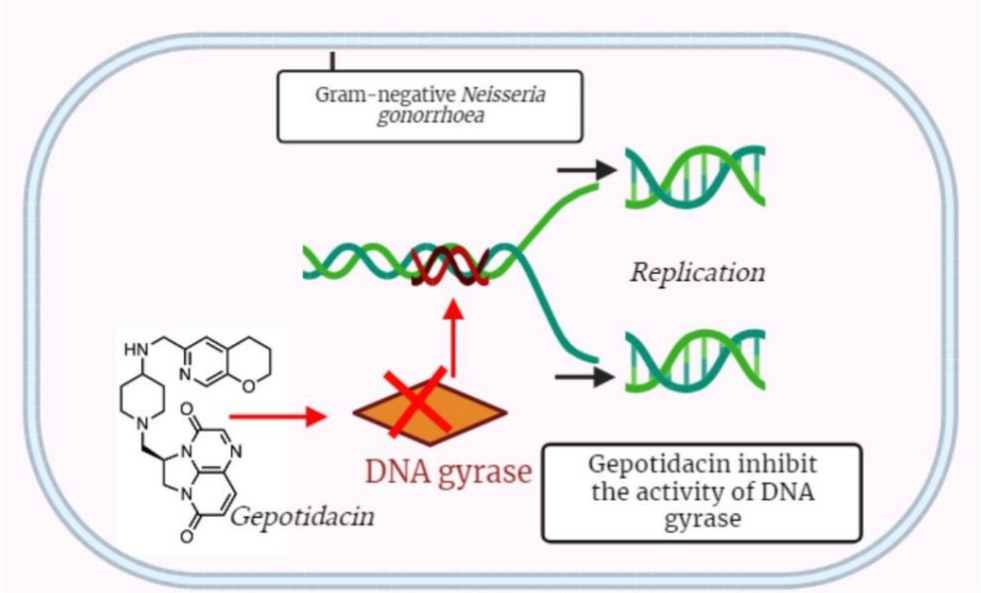


Figure 6: Gepotidacin functions by inhibiting the activity of gyrase in *N. gonorrhoea* and topoisomerase IV in gram-positive bacteria. This inhibition occurs through the formation of a complex involving the drug, the enzyme, and DNA. As a result, the drug is able to impede the normal functioning of these enzymes, leading to the generation of deadly double-stranded DNA breaks upon subsequent release. The breakage of these strands initiates the SOS response, which then triggers a DNA repair mechanism characterized by the involvement of low fidelity DNA synthesis. This process can result in the occurrence of deadly mutations, leading to genomic toxicity and ultimately culminating in cell death.

4.4. Zoliflodacin

In response to the persistent medical challenge posed by multi-drug resistance *N. gonorrheae*, researchers have created zoliflodacin, a novel class of antibacterial medicines referred to as spiropyrimidinetriones, with the aim of addressing simple gonorrhea. Zoliflodacin is an antibacterial medication that can be administered orally and exhibits bactericidal effects against bacterial type II topoisomerases. DNA topoisomerases are a class of enzymes found within cells that play a crucial role in the regulation of the three-dimensional conformation of DNA molecules within the nucleus. The differentiation between topoisomerase types I and II lies in their ability to create temporary single-or double-stranded breaks in DNA. Despite exhibiting significant similarities in sequence and structure, these enzymes serve separate roles in the process of DNA replication. Topoisomerase IV and DNA gyrase are a pair of closely affiliated DNA topoisomerase type II enzymes that play an essential role in DNA synthesis and serve as the primary targets of fluoroquinolones. These enzymes work together to induce changes in the structure of DNA throughout the process of replication. They begin by unwinding the tightly coiled DNA strands, then create temporary breaches in the double-stranded DNA, and finally reseal the breaks. DNA gyrase is a protein complex composed of two subunits, GyrA2-GyrB2, which functions to modulate the negative supercoiling of bacterial DNA. The decatenation (unlinking) of duplicated daughter chromosomes during replication is facilitated by TopoIV, which exists as a heterotetramer composed of ParC2 and ParE2 subunits (Bradford et al., 2020).

Zoliflodacin demonstrated a preferential inhibition of DNA formation over other macromolecules in logarithmically mature bacterial cells. Additionally, it stimulated the SOS response to DNA damage in Escherichia coli at levels comparable to ciprofloxacin. The inhibitory activity of zoliflodacin on bacterial topoisomerases was elucidated by its ability to hinder gyrase-mediated supercoiling and topoisomerase IV-mediated decatenation. Additionally, zoliflodacin was found to stabilize the enzyme-DNA cleaved complex for both gyrase and topoisomerase IV in purified *N. gonorrheae* enzymes. In contrast to ciprofloxacin, the religation process of cleaved

DNA was not observed in the presence of zoliflodacin when magnesium ions were absent from the DNA-gyrase-inhibitor complex (Bradford et al., 2020).

The primary focus of zoliflodacin in *N. gonorrheae* was found to be GyrB, as evidenced by a series of studies utilizing mutants at both the first and second steps. The incidence of zoliflodacin resistance was determined to be remarkably low in a single-step frequency analysis. Amino acid alterations in a conserved area of GyrB are observed in both first- and second-step mutants. Molecular modeling analysis revealed that the modifications leading to decreased susceptibility to zoliflodacin were located within the fluoroquinolone binding site. However, it should be noted that these mutations were primarily observed on the GyrB side of the pocket, in contrast to the more commonly reported fluoroquinolone mutations found on the opposite side in GyrA. Following the process of selecting for zoliflodacin resistance, a comparable series of mutations was observed in the gyrase of Staphylococcus aureus (Bradford et al., 2020).

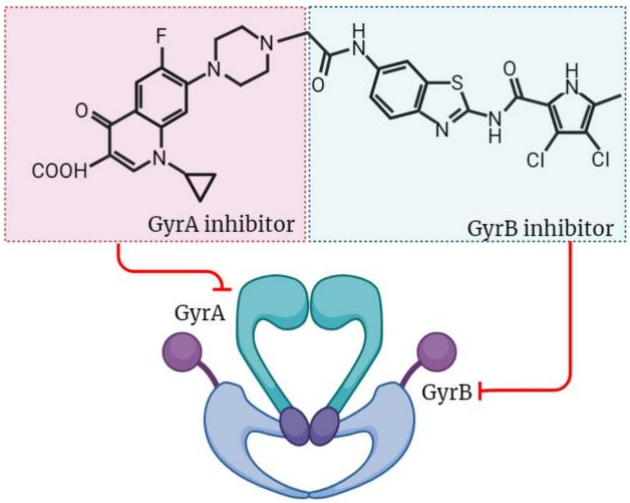


Figure 7: Zoliflodacin targets a “traditional” antibacterial mechanism in a novel way.

4.5. Solithromycin

Solithromycin is a fluoro-ketolide-based fourth-generation macrolide that was intended to replace telithromycin. Solithromycin has a similar structure to telithromycin. Solithromycin is more active against bacterial strains with the erm gene because it does not produce iMLSB-mediated rRNA methylation, it can inhibit cMLSB via the third binding site and the C3 ketone group, and it can adhere to the ribosome more strongly than the prior macrolide (Habiburrahman et al., 2020).

The 50S RNA proteins L4 and L22 normally bind to domain I of 23S rRNA, but mutations in these proteins can produce macrolide resistance by changing the conformation of domains II, III, and V, interrupting macrolide action on domain V of 23S rRNA. Previous research confirmed that mutations in the rrl gene inside the peptidyltransferase loop of domain V of the 23S rRNA generated macrolide resistance in *N. gonorrhoeae*. Solithromycin has a strong affinity for the major bacterial subunit ribosome, which is made up of rRNA residues. This initial contact can decrease protein synthesis by inhibiting polypeptide escape pathways via the exit tunnel. Biochemical analysis and X-ray crystallography reveal significant interactions between solithromycin and rRNA binding sites. Strong drug binding to the ribosome is caused by second contacts between the alkyl-aryl arm of solithromycin with base pairs and hydrogen bonding at the aminophenyl terminus with domain II rRNA 23S (Habiburrahman et al., 2020).

Furthermore, solithromycin binding at several bacterial ribosomal locations can help avoid antibiotic resistance. Solithromycin inhibits and interferes with bacterial protein synthesis with excellent selectivity. At a certain dose, solithromycin can suppress the production of bacterial firefly luciferase (Lux), but it has no impact on luciferase synthesis in the eukaryotic cell translational system. Solithromycin has the ability to interrupt cellular synthesis

and cause the generation of non-functional peptides. Because of these processes, solithromycin is bactericidal, unlike most other macrolide-grade antibiotics (Habiburrahman et al., 2020). (Figure 8)

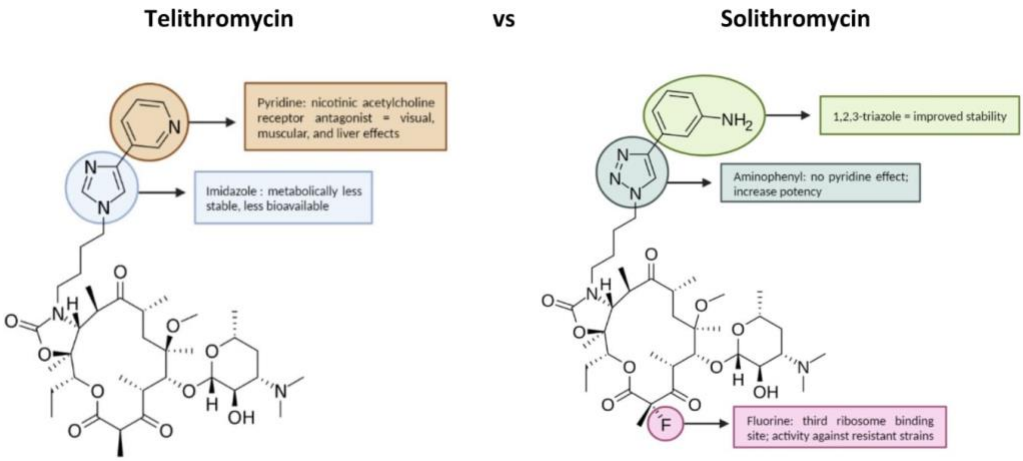


Figure 8: Solithromycin represents the initial instance of a "pure" ketolide. The recognition of the significance of incorporating a 2-F addition in solithromycin, resulting in increased activity against telithromycin-resistant bacteria, led to its classification as a fourth generation macrolide and the first fluoroketolid.

4.6. Tigecycline

Tigecycline, a member of the glycylcycline class of antibiotics, exerts its mechanism of action primarily by targeting the bacterial ribosome, specifically the 30S ribosomal subunit. The drug's unique structure allows it to bind to the ribosome in a manner distinct from traditional tetracyclines, offering increased potency against a wide range of pathogens, including multidrug-resistant organisms. Upon entering the bacterial cell, Tigecycline diffuses across the cytoplasmic membrane and reaches the ribosomes, which are responsible for protein synthesis. It binds to the A site of the 30S ribosomal subunit, preventing the binding of aminoacyl-tRNA, an essential component for the elongation of the growing peptide chain during translation. By doing so, Tigecycline effectively inhibits the incorporation of new amino acids into the nascent polypeptide chain, effectively halting protein synthesis (Yaghoubi et al., 2022). Moreover, Tigecycline exhibits a wide range of antimicrobial action, targeting both Gram-positive and Gram-negative bacteria. This includes very concerning pathogens like Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococcus (VRE), and Carbapenem-resistant Enterobacteriaceae (CRE) (Yaghoubi et al., 2022). (Figure 9)

A journal examining gonococcal isolates from China has tested the use of tigecycline as an alternative in the treatment of gonorrhea. The results showed that the mode and MIC90 (Minimal Inhibitory Concentration 90) of tigecycline (0.125 mg/L and 0.25 mg/L) were lower than those of doxycycline (1 mg/L and 16 mg/L) and tetracycline (2 mg/L and 64 mg/L). This suggests that tigecycline has stronger antimicrobial activity against gonococcal isolates, indicating the potential of this drug as an effective and reliable treatment option to overcome gonorrhea that is resistant to other antibiotics. These findings provide important insights in the effort to overcome antibiotic resistance and offer therapeutic alternatives that could potentially streamline the treatment of gonorrhea in the future (Yang et al., 2020).

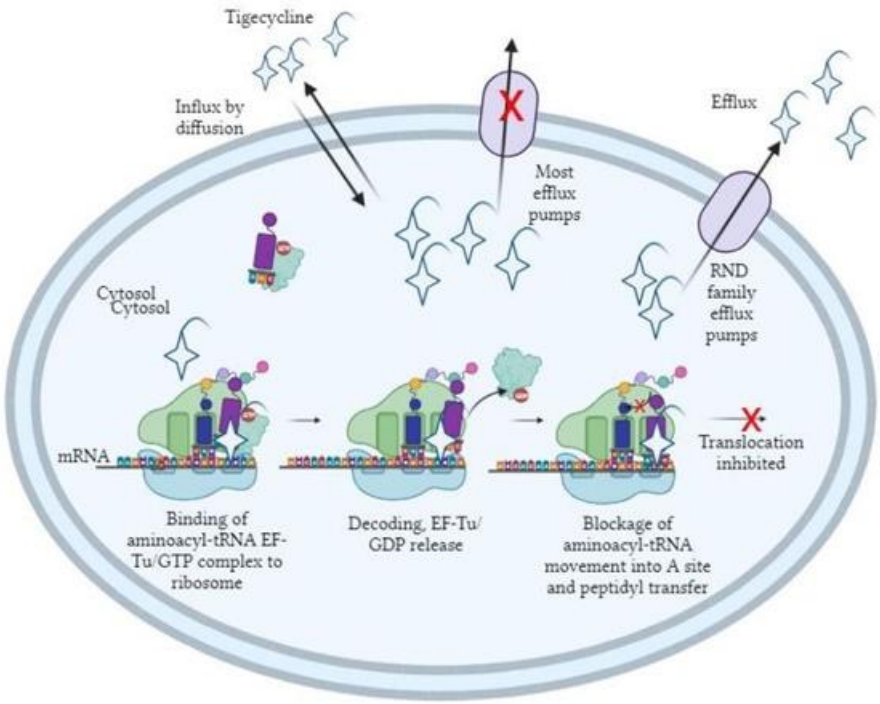


Figure 9: The disruption of protein synthesis leads to a cascade of events within the bacterial cell, ultimately resulting in impaired growth and replication. Tigecycline's ability to target the ribosomal subunit in this novel manner confers its effectiveness against bacteria that have developed resistance to other classes of antibiotics.

4.7. Ertapenem

Ertapenem, a member of the carbapenem class of antibiotics, exerts its mechanism of action by interfering with bacterial cell wall synthesis, leading to cell death. This β-lactam antibiotic demonstrates a broad-spectrum of activity against a diverse array of both Gram-positive and Gram-negative bacteria, rendering it a viable and efficacious therapeutic choice for a multitude of infections(*National Center for Biotechnology Information (2023)*, 2022).

The bactericidal activity of ertapenem is particularly effective against actively growing and dividing bacteria, making it a potent weapon against susceptible pathogens. Additionally, ertapenem demonstrates stability against many β-lactamases, including extended-spectrum β-lactamases (ESBLs) and some AmpC β-lactamases, which are enzymes responsible for antibiotic resistance. However, it is essential to note that ertapenem is not active against metallo-β-lactamases, such as New Delhi metallo-β-lactamase (NDM-1), which can confer resistance to carbapenems. Research has shown that ertapenem exhibits a strong affinity for various PBPs in Escherichia coli, including PBPs 1a, 1b, 2, 3, 4, and 5, with a specific preference for PBPs 2 and 3. By targeting these essential PBPs and inhibiting their transpeptidase activity, ertapenem disrupts peptidoglycan cross-linking in the bacterial cell wall, leading to damage and bacterial cell lysis. The wide spectrum of activity against various bacterial types, coupled with its ability to combat infections caused by multidrug-resistant pathogens, highlights ertapenem's potential as an effective therapeutic agent in the battle against antimicrobial resistance (Zhou et al., 2022).

A journal examining gonococcal isolates from China conducted a trial to evaluate the effectiveness of using tigecycline and ertapenem as alternatives in the treatment of gonorrhea. The results were interesting, with a mode and MIC90 (Minimal Inhibitory Concentration 90) of 0.03 mg/L and 0.06 mg/L respectively, ertapenem showed higher sensitivity than ceftriaxone (0.06 mg/L and 0.125 mg/L) and cefixime (0.06 mg/L and 0.125 mg/L) against these strains. These findings suggest tigecycline and ertapenem have the potential to be single or dual therapy options, possibly in combination with ceftriaxone, and should be considered for further sensitization studies and possibly further clinical trials. The use of these two antimicrobials as alternative gonorrhea treatment options could play an important role in addressing the issue of antibiotic resistance and improving the successful treatment of this infection (Yang et al., 2020).

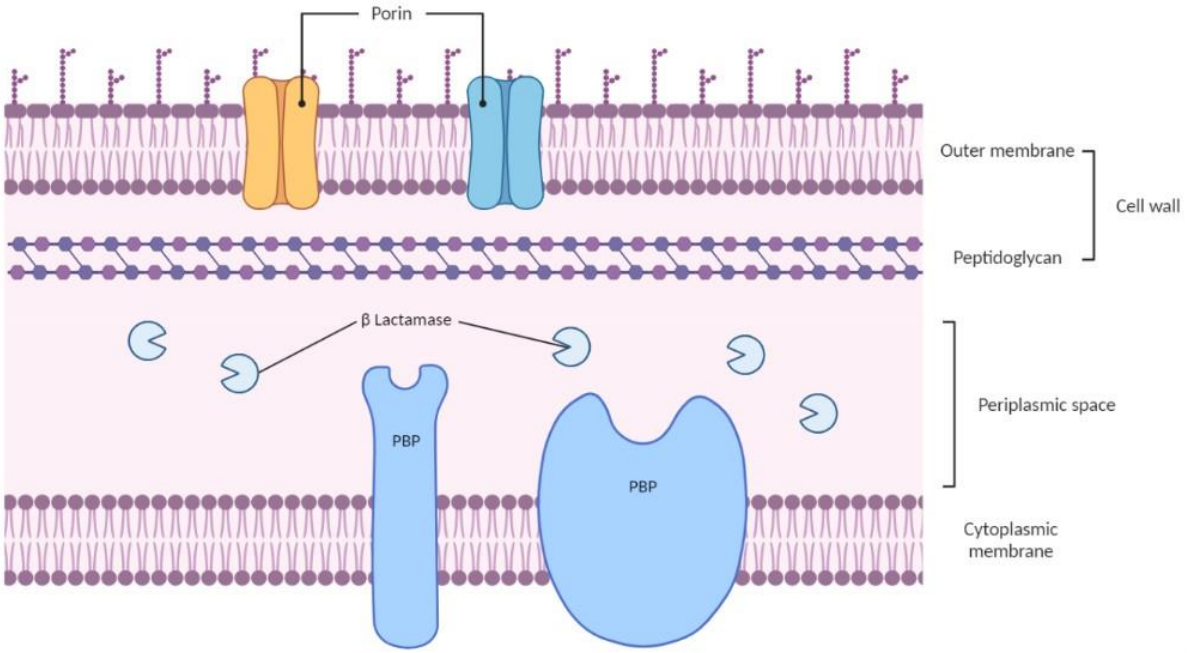


Figure 10: Upon entering the bacterial cell, ertapenem binds irreversibly to penicillin-binding proteins (PBPs), crucial enzymes involved in cell wall formation. Its high affinity for PBP-2, a transpeptidase responsible for cross-linking peptidoglycan chains, disrupts the cross-linking process and weakens the bacterial cell wall. As a result, cell wall damage occurs, followed by cell lysis, ultimately leading to bacterial death.

5. Various Efforts to Develop Types of Antibiotics to Prevent Resistance

The MtrCDE multidrug efflux pump is a significant factor in the development of gonococcal antimicrobial resistance, which results in non-specific resistance to many medications such as penicillins, cephalosporins, azithromycin, tetracyclines, ciprofloxacin, and other hydrophobic or amphipathic substances. Specifically, the emergence of multi-drug resistance in *N. gonorrhoeae* has been linked to certain mutations that suppress the MtrCDE efflux pump. These changes include adenine deletions in the promoter region of the mtrRCDE operon, as well as A39T or G45D polymorphisms in the MtrR protein. Furthermore, it has been observed that the mosaic mtrRCDE allele derived from Neisseria meningitidis and Neisseria commensal species plays a role in the development of multidrug resistance. It is worth noting that there has been a suggestion to sensitize *Neisseria gonorrhoeae* to currently available antibiotics and perhaps to antimicrobial chemicals produced by the human host by targeting MtrCDE through the suppression of its expression. Furthermore, it has been observed that alterations in the primary outer membrane porin not only decrease entry but also enhance efflux. The PorB1b protein has been demonstrated to enhance the level of resistance against penicillins, cephalosporins, and tetracyclines. Specifically, the introduction of mutations at positions G120 and A121 in the porin constriction zones, where bigger charged residues are substituted, has led to elevated levels of resistance (Golparian et al., 2014).

Efflux pumps are a class of membrane proteins responsible for the active transport of antibiotics out of bacterial cells, thereby ensuring the maintenance of low intracellular concentrations (Figure 11). The phenomenon of bacterial multidrug resistance (MDR) can be attributed to a decrease in the permeability of the outer membrane (OM), which subsequently leads to a lower uptake of drugs. The investigation conducted in the postgenomic era has provided evidence of the presence of a significant number of multidrug efflux pumps in bacterial organisms. Additionally, the structural analysis of co-crystals of multidrug efflux pumps has provided insights into the mechanisms by which these pumps recognize and export drugs, as well as the methods by which they can be inhibited. The ability of a single multidrug efflux pump to transport several drugs underscores the importance of finding efflux pump inhibitors as a critical strategy in addressing infectious illnesses resulting from multidrug-resistant bacteria (Giedraitienė et al., 2011).

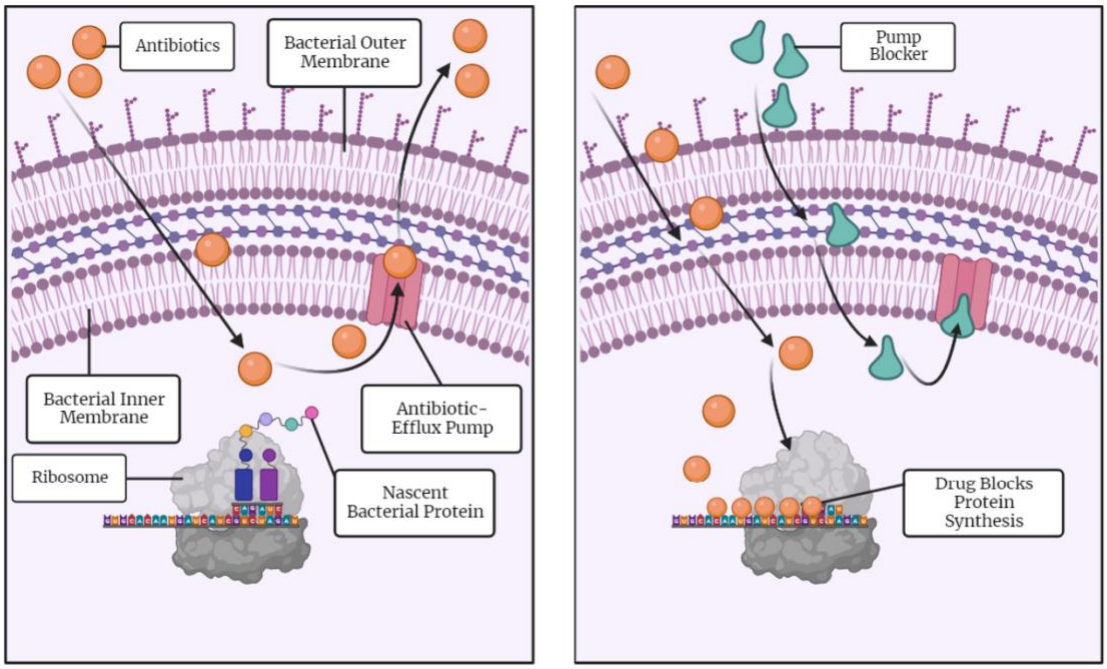


Figure 11: Multidrug efflux pumps refer to a class of inner membrane transporters that facilitate the exportation of several antibiotics from the intracellular environment to the extracellular space of bacterial cells. These pumps play a significant role in the development of bacterial multidrug resistance (MDR). The investigation conducted in the postgenomic era has provided evidence for the presence of a significant number of multidrug efflux pumps in bacterial organisms. Additionally, the structural analysis of co-crystals of multidrug efflux pumps has provided insights into the mechanisms by which these pumps recognize and export drugs, as well as the methods by which they can be inhibited. The exportation of numerous drugs can be facilitated by a single multidrug efflux pump. Therefore, the development of efflux pump inhibitors plays a key role in addressing infectious diseases that arise from bacteria with multidrug resistance. This review article elucidates the significance of multidrug efflux pumps in multidrug resistance (MDR), along with their physiological roles and inhibitory mechanisms.

6. Conclusion

Antimicrobial Resistance to sulfonamide, macrolides (such as azithromycin), penicillin, tetracycline, quinolones, and even ceftriaxone as a primary treatment option has been consistently observed in a substantial fraction of the gonococcal population for prolonged periods of time. In the event of the most severe outcome, gonorrhea has the potential to develop resistance to available treatments, rendering it untreatable.

Zoliflodacin a new class of antibacterial drugs known as spiropyrimidinetriones, is an orally accessible antibacterial drug with bactericidal activity against bacterial type II topoisomerases. DNA topoisomerases are enzymes in cells that regulate the three-dimensional structure of DNA inside DNA. Tigecycline, offers increased potency against a wide range of pathogens, including multidrug-resistant organisms. Upon entering the bacterial cell, tigecycline diffuses across the cytoplasmic membrane and reaches the ribosomes, which are responsible for protein synthesis and effectively inhibit the incorporation of new amino acids into the nascent polypeptide chain. Zoliflodacin, tigecycline, and ertapenem in single or dual therapy with ceftriaxone could be considered as a potential option for treating gonorrhea resistant to antibiotics. Gentamicin cannot be recommended to replace ceftriaxone as first-line therapy. Gepotidacin is effective for GyrA A92T mutation in gonorrhea infection.

The phenomenon of bacterial multidrug resistance (MDR) can be attributed to a decrease in the permeability of the outer membrane (OM), which subsequently leads to a lower uptake of drugs. The investigation conducted in the postgenomic era has provided evidence of the presence of a significant number of multidrug efflux pumps in bacterial organisms.

References

Bereda, G. (2022). Clinical Pharmacology of Ceftriaxone in Paediatrics. *Journal of Biomedical and Biological Sciences*, *2*(1), 1–8.

Bradford, P. A., Miller, A. A., O'Donnell, J., & Mueller, J. P. (2020). Zoliflodacin: An Oral Spiropyrimidinetrione Antibiotic for the Treatment of Neisseria gonorrheae, including Multi-Drug-Resistant Isolates. *ACS Infectious Diseases*, *6*(6), 1332–1345. https://doi.org/10.1021/acsinfecdis.0c00021

Campbell, D. J., & Ed, F. R. C. P. (1944). GONORRHOEA IN NORTH AFRICA AND THE. *Br Med J*, *2*(Jul 8), 44. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2285755/

Chen, M. Y., McNulty, A., Avery, A., Whiley, D., Tabrizi, S. N., Hardy, D., Das, A. F., Nenninger, A., Fairley, C. K., Hocking, J. S., Bradshaw, C. S., Donovan, B., Howden, B. P., & Oldach, D. (2019). Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial. *The Lancet Infectious Diseases*, *19*(8), 833–842. https://doi.org/10.1016/S1473-3099(19)30116-1

Coates, A. R. M., Hu, Y., Holt, J., & Yeh, P. (2020). Antibiotic combination therapy against resistant bacterial infections: synergy, rejuvenation and resistance reduction. *Expert Review of Anti-Infective Therapy*, *18*(1), 5–15. https://doi.org/10.1080/14787210.2020.1705155

Costa-Lourenço, A. P. R. da, Barros dos Santos, K. T., Moreira, B. M., Fracalanzza, S. E. L., & Bonelli, R. R. (2017). Antimicrobial resistance in Neisseria gonorrhoeae: history, molecular mechanisms and epidemiological aspects of an emerging global threat. *Brazilian Journal of Microbiology*, *48*(4), 617–628. https://doi.org/10.1016/j.bjm.2017.06.001

Darby, E. M., Trampari, E., Siasat, P., Gaya, M. S., Alav, I., Webber, M. A., & Blair, J. M. A. (2023). Molecular mechanisms of antibiotic resistance revisited. *Nature Reviews Microbiology*, *21*(5), 280–295. https://doi.org/10.1038/s41579-022-00820-y

Doi, Y., Wachino, J., & Arakawa, Y. (2017). HHS Public Access Author manuscript Infect Dis Clin North Am. Author manuscript; available in PMC 2017 June 01. Published in final edited form as: Infect Dis Clin North Am. 2016 June ; 30(2): 523–537. doi:10.1016/j.idc.2016.02.011. Aminoglycoside Resistan. *Physiology & Behavior*, *176*(10), 139–148. https://doi.org/10.1016/j.idc.2016.02.011.Aminoglycoside

Fenton, B. A., Tomberg, J., Sciandra, C. A., Nicholas, R. A., Davies, C., & Zhou, P. (2021). Mutations in PBP2 from ceftriaxone-resistant Neisseria gonorrhoeae alter the dynamics of the β3–β4 loop to favor a low-affinity drug-binding state. *Journal of Biological Chemistry*, *279*(4), 101188. https://doi.org/10.1016/j.jbc.2021.101188

Giedraitienė, A., Giedraitienė, A., Vitkauskienė, A., Naginienė, R., & Pavilonis, A. (2011). Correspondence to Antibiotic Resistance Mechanisms of Clinically Important Bacteria. *REVIEW Medicina (Kaunas)*, *47*(3), 137–183.

Golparian, D., Shafer, W. M., Ohnishi, M., & Unemo, M. (2014). Importance of multidrug efflux pumps in the antimicrobial resistance property of clinical multidrug-resistant isolates of neisseria gonorrhoeae. *Antimicrobial Agents and Chemotherapy*, *58*(6), 3556–3559. https://doi.org/10.1128/AAC.00038-14

Habiburrahman, M., Soetikno, V., Sirait, W. R., & Savira, M. (2020). Solithromycin as a potential novel antibiotic against Neisseria gonorrhoeae resistance. *Indonesian Journal of Pharmacy*, *31*(4), 335–353. https://doi.org/10.22146/ijp.1123

Hathorn, E., Dhasmana, D., Duley, L., & Ross, J. D. C. (2014). The effectiveness of gentamicin in the treatment of Neisseria gonorrhoeae: A systematic review. *Systematic Reviews*, *3*(1), 1–9. https://doi.org/10.1186/2046-4053-3-104

Holley, C. L., Dhulipala, V., Balthazar, J. T., Van, A. Le, Begum, A. A., Chen, S. C., Read, T. D., Matoga, M., Hoffman, I. F., Golparian, D., Unemo, M., Jerse, A. E., & Shafer, W. M. (2022). A Single Amino Acid Substitution in Elongation Factor G Can Confer Low-Level Gentamicin Resistance in Neisseria gonorrhoeae. *Antimicrobial Agents and Chemotherapy*, *66*(5), 1–11. https://doi.org/10.1128/aac.00251-22

Hooper, D. C., & Jacoby, G. A. (2016). *Mechanisms of Action and Resistance*. 1–21.

Lambert, P. A. (2005). Bacterial resistance to antibiotics: modified target sites. *Advanced Drug Delivery Reviews*, *57*(10), 1471–1485. https://doi.org/10.1016/j.addr.2005.04.003

Lawrence, A., Phillips, I., & Nicol, C. (1973). Various regimens of trimethoprim-sulfamethoxazole used in the treatment of gonorrhea. *Journal of Infectious Diseases*, *128*(November), S673–S678. https://doi.org/10.1093/infdis/128.Supplement_3.S673

Liu, J. W., Xu, W. Q., Zhu, X. Y., Dai, X. Q., Chen, S. C., Han, Y., Liu, J., Chen, X. S., & Yin, Y. P. (2019). Gentamicin susceptibility of neisseria gonorrhoeae isolates from 7 provinces in China. *Infection and Drug Resistance*, *12*, 2471–2476. https://doi.org/10.2147/IDR.S214059

Lobanovska, M., & Pilla, G. (2017). Penicillin's discovery and antibiotic resistance: Lessons for the future? *Yale Journal of Biology and Medicine*, *90*(1), 135–145.

Masi, M., & Pagès, J.-M. (2013). Structure, Function and Regulation of Outer Membrane Proteins Involved in

Drug Transport in Enterobactericeae: the OmpF/C – TolC Case. *The Open Microbiology Journal*, *7*(1), 22–33. https://doi.org/10.2174/1874285801307010022

Mlynarczyk-Bonikowska, B., Kowalewski, C., Krolak-Ulinska, A., & Marusza, W. (2022). Molecular Mechanisms of Drug Resistance and Epidemiology of Multidrug-Resistant Variants of Neisseria gonorrhoeae. *International Journal of Molecular Sciences*, *23*(18). https://doi.org/10.3390/ijms231810499

National Center for Biotechnology Information (2023). (2022). PubChem Compound Summary for CID 150610.

Ross, J. D. C., Brittain, C., Cole, M., Dewsnap, C., Harding, J., Hepburn, T., Jackson, L., Keogh, M., Lawrence, T., Montgomery, A. A., Roberts, T. E., Sprange, K., Tan, W., Thandi, S., White, J., Wilson, J., & Duley, L. (2019). Gentamicin compared with ceftriaxone for the treatment of gonorrhoea (G-ToG): a randomised non-inferiority trial. *The Lancet*, *393*(10190), 2511–2520. https://doi.org/10.1016/S0140-6736(18)32817-4

Ross, J. D. C., Harding, J., Duley, L., Montgomery, A. A., Hepburn, T., Tan, W., Brittain, C., Meakin, G., Sprange, K., Thandi, S., Jackson, L., Roberts, T., Wilson, J., White, J., Dewsnap, C., Cole, M., & Lawrence, T. (2019). Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: The G-TOG non-inferiority RCT. *Health Technology Assessment*, *23*(20), 1–103. https://doi.org/10.3310/hta23200

Scangarella-Oman, N. E., Hossain, M., Dixon, P. B., Ingraham, K., Min, S., Tiffany, C. A., Perry, C. R., Raychaudhuri, A., Dumont, E. F., Huang, J., Hook, E. W., & Miller, L. A. (2018). Microbiological analysis from a phase 2 randomized study in adults evaluating single oral doses of gepotidacin in the treatment of uncomplicated urogenital gonorrhea caused by neisseria gonorrhoeae. *Antimicrobial Agents and Chemotherapy*, *62*(12), 1–34. https://doi.org/10.1128/AAC.01221-18

Shafran, S. D. (1990). The basis of antibiotic resistance in bacteria. *Journal of Otolaryngology*, *19*(3), 158–168.

Stratton, C. W. (2000). Mechanisms of bacterial resistance to antimicrobial agents. *Journal Medical Libanais*, *48*(4), 186–198. https://doi.org/10.1128/microbiolspec.arba-0019-2017

Tapsall, J. W., Ndowa, F., Lewis, D. A., & Unemo, M. (2009). Meeting the public health challenge of multidrug- and extensively drug-resistant Neisseria gonorrhoeae. *Expert Review of Anti-Infective Therapy*, *7*(7), 821–834. https://doi.org/10.1586/ERI.09.63

Taylor, S. N., Marrazzo, J., Batteiger, B. E., Hook, E. W., Seña, A. C., Long, J., Wierzbicki, M. R., Kwak, H., Johnson, S. M., Lawrence, K., & Mueller, J. (2018). Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea. *New England Journal of Medicine*, *379*(19), 1835–1845. https://doi.org/10.1056/nejmoa1706988

Tewabe, A., Marew, T., & Birhanu, G. (2021). The contribution of nano-based strategies in overcoming ceftriaxone resistance: a literature review. *Pharmacological Research*, *9*(4). https://doi.org/https://doi.org/10.1002/prp2.849

Uddin, T. M., Chakraborty, A. J., Khusro, A., Zidan, B. R. M., Mitra, S., Emran, T. Bin, Dhama, K., Ripon, M. K. H., Gajdács, M., Sahibzada, M. U. K., Hossain, M. J., & Koirala, N. (2021). Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. *Journal of Infection and Public Health*, *14*(12), 1750–1766. https://doi.org/10.1016/j.jiph.2021.10.020

Unemo, M., & Shafer, W. M. (2014). Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution, and future. *Clinical Microbiology Reviewa*, *27*(3), 587–613. https://doi.org/10.1128/CMR.00010-14.

Urban-Chmiel, R., Marek, A., Stępień-Pyśniak, D., Wieczorek, K., Dec, M., Nowaczek, A., & Osek, J. (2022). Antibiotic Resistance in Bacteria—A Review. *Antibiotics*, *11*(8). https://doi.org/https://doi.org/10.3390/antibiotics11081079

Varela, M. F., Stephen, J., Lekshmi, M., Ojha, M., Wenzel, N., Sanford, L. M., Hernandez, A. J., Parvathi, A., & Kumar, S. H. (2021). BacVarela, M. F. et al. (2021) 'Bacterial Resistance to Antimicrobial Agents'.terial Resistance to Antimicrobial Agents. *Antibiotics*, *10*, 593.

WHO. (2016). *Global action plan on antimicrobial resistance*. World Health Organization.

Xu, W., Zhou, Q., Liu, J., Zhang, Y., Zhu, X., Zhu, B., & Yin, Y. (2022). In Vitro Study of the Interaction of Gentamicin with Ceftriaxone and Azithromycin against Neisseria gonorrhoeae Using Agar Dilution Method. *Antibiotics*, *11*(8). https://doi.org/10.3390/antibiotics11081083

Yaghoubi, S., Zekiy, A. O., Krutova, M., Gholami, M., Kouhsari, E., Sholeh, M., & Ghafouri, Z. F. M. (2022). Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review. *European Journal of Clinical Microbiology*, *41*(7), 1003–1022. https://doi.org/10.1007/s10096-020-04121-1

Yang, F., Yan, J., Zhang, J., & Veen, S. van der. (2020). Evaluation of alternative antibiotics for susceptibility of gonococcal isolates from China. *International Journal of Antimicrobial Agents*, *55*(2). https://doi.org/10.1016/j.ijantimicag.2019.11.003.

Zarantonelli, L., Borthagaray, G., Lee, E. H., & Shafer, W. M. (1999). Decreased azithromycin susceptibility of Neisseria gonorrhoeae due to mtrR mutations. *Antimicrobial Agents and Chemotherapy*, *43*(10), 2468–2472. https://doi.org/10.1128/aac.43.10.2468

Zhou, C.-C., Huang, F., Zhang, J.-M., & Zhuang, Y.-G. (2022). Population Pharmacokinetics of Tigecycline: A Systematic Review. *Drug Design, Development, and Therapy*, *17*, 1885–1896.

https://doi.org/10.2147/DDDT.S365512.