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Review

Treatment of Sexually Transmitted Infections (STIs) Caused by *Neisseria gonorrhoeae* and the Global Shortage of Antibiotics

José Luis Rodrigues Martins [1], Emerith Mayra Hungria Pinto [1], Salomão Antonio Oliveira [1], Fernanda Almeida Costa Gomes [1] and Osmar Nascimento Silva [1,2,*]

[1] Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Evangélica de Goiás, Anápolis 75083-515, Brazil
[2] Facultad de Medicina, Universidad Sudamericana, Pedro Juan Caballero 8500, Paraguay
* Correspondence: osmar.silva@catolica.edu.br; Tel.: +55-62-3310-6684

Abstract: The gonorrhoea caused by the bacterium *Neisseria gonorrhoeae* remains a major global public health problem with high morbidity. Gonorrhoea can affect both women and men, being more prevalent in sexually active young individuals. Even after infection from *N. gonorrhoeae*, many patients may remain asymptomatic, making the diagnosis and adequate treatment of the disease difficult. The treatment and control of gonorrhoea have been difficult in recent years in most populations, being an example of how behavioural, social, and demographic factors can influence the epidemiology of an infectious disease. The emergence of strains of *N. gonorrhoeae* resistant to multiple antimicrobials, especially to extended-spectrum cephalosporins, indicates that gonorrhoea has the potential to become untreatable in the current reality of treatment options, especially in places that have a high prevalence of gonococcal infections. The loss of available and effective treatment options can lead to significant increases in new cases of the disease, as well as increased morbidity and mortality. This review provides an overview of current therapeutic options for gonorrhoea, as well as ongoing experimental studies and clinical trials with new antigonococcal agents.

Keywords: antimicrobial resistance; multidrug resistance; new therapy; dual antimicrobial therapy; drug repurposing; gonorrhoea; *Neisseria gonorrhoeae*

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Citation: Martins, J.L.R.; Pinto, E.M.H.; Oliveira, S.A.; Gomes, F.A.C.; Silva, O.N. Treatment of Sexually Transmitted Infections (STIs) Caused by *Neisseria gonorrhoeae* and the Global Shortage of Antibiotics. *Venereology* **2022**, *1*, 235–244. https://doi.org/10.3390/venereology1030017

Academic Editor: Alessandro Russo

Received: 27 June 2022
Accepted: 17 October 2022
Published: 24 October 2022

1. Introduction

Sexually transmitted infections (STIs) are among the most important public health problems worldwide [1]. Although the magnitude of the STIs is not known, it is believed that, in developing countries, it is one of the main reasons for seeking healthcare services [2]. In the year 2020, the World Health Organisation (WHO) estimated ~374 million annual cases worldwide, i.e., a daily average of ~1 million cases per year of the four curable STIs, syphilis (~129 million), gonorrhoea (~82 million), syphilis (~7.1 million), and trichomoniasis (~156 million) [3].

STIs have consistently been a matter of concern for decades now. The AIDS epidemic and the advent of dating apps have helped bring to light the significant public health threat posed by STIs [4,5].

Gonorrhoea is the third most prevalent STI, and its control is globally challenging, particularly due to antimicrobial resistance and poor antimicrobial stewardship, being an example of the influence that social, behavioural, and demographic factors exert on the epidemiology of STIs [6]. Gonorrhoea is an infectious disease of global distribution, transmitted almost exclusively by sexual or perinatal contact, caused by the bacterium *N. gonorrhoeae* which has adapted to be an exclusive pathogen of *Homo sapiens*. It is capable of producing localised urogenital, rectal, oropharyngeal, and systemic diseases. Although the highest incidence occurs in developing countries, rates of the disease are high in developed countries, and numbers have remained high in recent years with an increasing

trend, especially among marginalised vulnerable populations associated with ethnicity or sexual orientation [7]. The cause for high rates of gonorrhoea may be related to numerous factors, including a large number of cases where the disease is asymptomatic, especially in males [8], self-medication [9,10], and the difficulty in access to screening tests, especially in developing countries [11], in addition to cultural factors, where many people fail to seek medical care for fear of being discriminated against [12,13].

Clinical Presentation of Gonorrhoea

In men, the typical clinical manifestations of acute urethritis begin after an average incubation period of ~2–5 days [14]. In symptomatic infections, symptoms may initially present as a tingling sensation/itchy urethra, with dysuria; ~2 to 3 days later, there is a mucous urethral discharge, which quickly becomes purulent mucus, yellow-green in colour, with abundant and spontaneous elimination. The edges of the urethral meatus may become swollen and the mucosa erythematous. Swelling of the foreskin may occur, and inflammatory phimosis may develop. Often, the incubation period in gonorrhoea is shorter compared to nongonococcal urethritis, dysuria may be more prominent, and urethral discharge may be more profuse and purulent [15]. A small proportion of men with urethral gonorrhoea may be asymptomatic or oligosymptomatic. This fact can be related to the type of infecting strain; some serotypes are more associated with asymptomatic infections [16].

In women, the endocervical canal is the primary site of gonococcal infection. The urethra, rectum, and Bartholin's glands may also be affected with disease progressing with minimal symptoms characterised by a scarce, milky discharge, often imperceptible by the patient [15]. In many cases, this lack of symptoms may preclude clinical diagnosis of gonorrhoea in women; however, when associated with anamnesis, it can increase the chances of suspecting the infection [17]. In addition, an infection can lead to inflammation of the fallopian tubes and ovaries, which, when left untreated, may characterise the pelvic inflammatory disease, representing the most important complication of gonococcal disease in women [18]. During pregnancy, gonorrhoea is associated with first-trimester miscarriage, preterm birth, and infant mortality [15,17].

2. Treatment of Gonorrhoea

The treatment of patients with gonococcal urethritis should be started early, to interrupt the chain of transmission, reduce the discomfort of clinical manifestations, and prevent systemic complications of the infection [19]. However, it should be considered that antimicrobial susceptibility patterns vary according to the geographic area or population studied and fluctuate over time, and the treatment recommendation should be monitored according to antimicrobial resistance and surveillance data, where available [20]. A worrying factor related to STIs is the increase in the identification/occurrence of strains of *N. gonorrhoeae* resistant to multiple antibiotics, which reduces treatment options [21]. In this scenario, constant laboratory monitoring and replacement of therapeutic recommendations becomes necessary, requiring the use of more expensive drugs. This fact has financial repercussions, and these antibiotics with higher costs are often inaccessible in developing countries where the highest incidence of the disease is found [22,23].

The control of gonorrhoea is an essential public health issue, requiring an integrated approach in which the provision of effective treatment is essential to interrupt the transmission chain and reduce the impact of the disease [24,25]. Gonorrhoea requires continuous and efficient surveillance of resistance [26]. Regional information is important for adapting treatment regimens to different geographic regions, and it is insufficient and unacceptable to rely on data obtained from other regions to arrive at the best treatment option [27,28]. Many people who have gonorrhoea may have no symptoms; therefore, a timely diagnosis is required through routine screening for gonorrhoea, with rapid and effective treatment [17,28].

The antimicrobial treatment performed in many countries is empirical therapy, at the first health visit for the management of *N. gonorrhoeae* infection, with a dual therapy of antibiotics, mainly a third-generation cephalosporin and a macrolide (Table 1) [17,29,30]. In settings where local resistance data are not available, the empirical first-line therapy for uncomplicated anogenital and pharyngeal gonorrhoea comprises a dual regimen, with a single dose of ceftriaxone or cefixime plus azithromycin. This dual therapy was introduced to resolve the problem of frequent *Chlamydia trachomatis* coinfection, in addition to the fact that combination therapy can reduce the emergence of antimicrobial resistance [26,30].

The divergence between the use of monotherapy and dual therapy in the first-line treatment for gonorrhoea has been accentuated in recent years, in view of the increasing report of strains resistant to cephalosporins and azithromycin [31,32]. The justification for the dual approach is to address coinfection by *C. trachomatis*, which occurs in 10–40% of individuals with urogenital gonorrhoea, as well as a hypothetical benefit of reducing the onset and/or spread of antimicrobial resistance (particularly resistance to ceftriaxone) in *N. gonorrhoeae* [25,30,33,34].

Protocols for the treatment of gonorrhoea show significant differences across countries, taking into account drug availability and local evidence of susceptibility of *N. gonorrhoeae* to antimicrobials (Table 1). For the treatment of uncomplicated gonococcal infection, the Brazilian protocol recommends the combination therapy of ceftriaxone 500 mg (IM), plus azithromycin 1 g (PO), both in a single dose for uncomplicated gonococcal infections. The CDC recommends monotherapy with ceftriaxone 500 mg (IM) in a single dose [35–38].

To stop the chain of transmission of gonorrhoea, it is critical that the sexual partners of infected people are treated. Therefore, this information must be passed on to the patient with gonorrhoea, while providing communication tools. The sexual partner must be instructed to seek a health unit, and, when arriving at the health service, the partner must be considered to have the same infection that affected the index case, even if there is no sign or symptom, and receive the same treatment. Sexual partnerships of pregnant women with gonorrhoea and pregnant partners of people with gonorrhoea who do not respond to communication for treatment should be prioritised for active search [15].

In the US, the treatment of sexual partners, known as expedited partner therapy (EPT) is recommended in 43 states, which is achieved through the IM administration of ceftriaxone 500 mg. Despite the high financial cost involved, treating sexual partners is extremely important; studies show that approximately 30% of gonorrhoea cases are asymptomatic [39,40].

No robust studies were found that calculate the total effective costs; however, in a study carried out in the United States where quality-adjusted life-years (QALYs) were used as a parameter, the value found was less than 13,000 USD for women regardless of age, independent of percentage of partners who sought service from the same payer [39,41], where this value for a QALY is considered low [42].

Table 1. Summary of current guidelines for the treatment of *Neisseria gonorrhoeae* recommended by the WHO, CDC, and Brazilian and UK governments.

	Therapeutic Scheme in a Single Dose					
	WHO	**Brazil**	**CDC EUA**			**UK**
Uncomplicated gonococcal infection of the cervix, urethra, or rectum	Ceftriaxone 250 mg intramuscular (IM) + Azithromycin 1 g orally OR Cefixime 400 mg orally + Azithromycin 1 g orally If recent local resistance data confirming susceptibility to the antimicrobial: Ceftriaxone 250 mg IM OR Cefixime 400 mg orally OR Spectinomycin 2 g IM	Ceftriaxone 500 mg IM + Azithromycin 1 g orally ***	Ceftriaxone 500 mg IM for persons weighing <150 kg * OR Ceftriaxone 1 g IM for persons weighing ≥150 kg *	Alternative Regimens: Gentamicin 240 mg IM + Azithromycin 2 g orally If ceftriaxone administration is not available or not feasible: Cefixime 800 mg orally *	Ceftriaxone 1 g IM **** OR Ciprofloxacin 500 mg orally ***** Alternative Regimens ******	Cefixime 400 mg orally + Azithromycin 2 g orally OR Gentamicin 240 mg IM + Azithromycin 2 g orally OR Spectinomycin 2 g + Azithromycin 2 g orally
Uncomplicated gonococcal infection of the pharynx	Ceftriaxone 250 mg IM + Azithromycin 1 g orally OR Cefixime 400 mg orally + Azithromycin 1 g orally If recent local resistance data confirming susceptibility to the antimicrobial: Ceftriaxone 250 mg IM	Ceftriaxone 500 mg IM + Azithromycin 1 g orally ***	Ceftriaxone 500 mg IM for persons weighing <150 kg ** OR Ceftriaxone 1 g IM for persons weighing ≥150 kg **		Ceftriaxone 1 g IM **** OR Ciprofloxacin 500 mg orally *****	Cefixime 400 mg orally + Azithromycin 2 g orally OR Gentamicin 240 mg IM + Azithromycin 2 g orally

* If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days. ** If chlamydial infection is identified when pharyngeal gonorrhoea testing is performed, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days. *** In case of chlamydia or mycoplasma infection, treat with azithromycin 1 g single dose OR doxycycline 100 mg orally 2 times/day for 7 days (except pregnant). **** When antimicrobial susceptibility is not known prior to treatment. ***** When antimicrobial susceptibility is known prior to treatment, with care recommendations. ****** Alternative regimens may be given because of allergy, needle phobia, or other absolute or relative contraindications.

2.1. Current Treatment Options for Multidrug-Resistant N. gonorrhoeae

In recent years, the number of strains of *N. gonorrhoeae* resistant to multiple drugs has increased, which has reduced the therapeutic options [43]. Sulphonamides were introduced as the first therapy for gonorrhoea during the 1940s; however, sulphonamide-resistant strains were isolated 4 years later in 1944 [44]. Sulphonamides bind to bacterial dihydropteroate synthase (DHPS) enzymes, inhibiting folic acid synthesis [45]. Sulphonamide resistance may be mediated by excessive synthesis of *p*-aminobenzoic acid, which dilutes the antimicrobial agent, or by alterations in the folP gene [43]. DHPS changes result in significantly reduced affinity for sulphonamides and bacteriostatic activity [45].

In 1943, penicillin began to be used for the treatment of gonorrhoea, and it soon became the treatment of choice as gonococci were highly susceptible to penicillin [46,47]. However, in 1946, the first cases of *N. gonorrhoeae* resistant to high doses of penicillin (1.6 million units) were reported [43]. The resistance to beta-lactams described so far is mediated by genes located on chromosomes or plasmids. The most frequent plasmid resistance mechanism occurs via *bla*TEM-1, which encodes a TEM-1 beta-lactamase enzyme that opens the beta-lactam ring, rendering penicillin inactive [48]. The chromosomal resistance mechanism of *N. gonorrhoeae* against beta-lactams is due to mutations in penicillin-binding proteins (PBPs). These changes increase the efflux and decrease the bacteria's permeability to beta-lactams. The most frequent mutations occur in the *penA*, *ponA1*, *penB*, *penC*, and *mtrR* genes, which encode PBP2, which is the main target for beta-lactam antibiotics, consequently decreasing the susceptibility of *N. gonorrhoeae* to penicillin [49].

The mechanisms of chromosome-mediated penicillin resistance are not fully understood. Some mechanisms already elucidated include mutations in the promoter region of the *mtrR* gene resulting in overexpression of the MtrC–MtrD–MtrE efflux pump, reduced permeability of the outer membrane protein PorB1b, probable mutations in *pilQ*, the gene which encodes secretory proteins, and mutations in *penA*, which promote modifications in PBP2, decreasing the rate of penicillin acylation, in addition to creating the PBP2 mosaic, which reduces susceptibility and/or contributes to treatment failure with cefixime and ceftriaxone, as well as the determinant *porA*, which encodes mutations in PBP1, action similar to the *penA* determinant [50–52] (for a more detailed review of the mechanisms of resistance to beta-lactams, consult the article [53]).

Tetracycline was introduced in the 1950s to target patients allergic to penicillin [54]. Tetracyclines act by reversibly binding to the 30S subunit of the ribosome, blocking the binding of transfer RNA, preventing protein synthesis, resulting in a bacteriostatic effect [55]. The resistance of *N. gonorrhoeae* to tetracycline is chromosomally mediated and results from a combination of three genetic mutations that resemble beta-lactam resistance (i) *mtrR* mutation, which results in the overexpression of efflux pump MtrC–MtrD–MtrE, (ii) the *penB* determinant, which results in a porin mutation that decreases the influx of tetracycline into the cell, and (iii) the *rpsJ* allele, which encodes an altered form of ribosomal protein [56]. Of the mechanisms described, the *rpsJ1* determinant is the only one specific (to date) for tetracycline resistance, making it the first specific resistance gene identified for this antimicrobial in chromosomally mediated tetracycline-resistant gonococcal strains.

In the mid-1980s, fluoroquinolones, especially ciprofloxacin, became widely used for the treatment of gonorrhoea [43]. Quinolones act by inhibiting DNA gyrase and topoisomerase IV, two essential topoisomerases for DNA replication, transcription, recombination, and repair, resulting in bactericidal activity [57]. As with the previously described antibiotic classes, a few years after their use on a global scale, strains resistant to fluoroquinolones have been described worldwide. Currently, three mechanisms of resistance to quinolones have been described: (i) mutations that alter drug targets, (ii) mutations that reduce drug accumulation, and (iii) plasmids that protect bacterial cells from the lethal effects of quinolones [58]. In 2007, ciprofloxacin left the list of drugs recommended by the CDC for the treatment of gonorrhoea.

Following the disuse of fluoroquinolones, most countries changed their therapeutic guidelines, including the use of third-generation cephalosporins as first-line therapy for the treatment of gonorrhoea [59]. Like other beta-lactam antibiotics, cephalosporins interfere with peptidoglycan cell-wall synthesis via inhibition of PBPs. Thus, via the inhibitory action on cell-wall synthesis, the bacterium undergoes osmotic lysis. The mechanisms of resistance to cephalosporins are related to the penA mosaic that encode PBP2s enzymes with a reduced rate of PBP2 acylation [60].

As described above the primary problem with treatment of gonorrhoea is the continual development of multidrug-resistant strains of *N. gonorrhoeae*, combined with the lack of development of new antimicrobials [61]. The process of developing new antibiotics is expensive and laborious, since, for each drug that reaches the market as a successful drug, the industry often has to screen a high number of compounds. Another aggravating factor, compared to continuous-use drugs, is that developing new antibiotics, which will be used in exceptional cases of infections and for a short period of time, is not economically viable. Therefore, companies are failing to invest in the selection and development of new antibiotics, unless they receive state incentives.

In view of the scenario described above, alternative regimens with ciprofloxacin may be an option if the strain is considered susceptible after phenotypic or genetic testing [62]. Alternatives include high-dose (2 g) azithromycin monotherapy or spectinomycin, and gentamicin (both together with high-dose azithromycin) [35]. A study conducted in Brazil indicated the absence of *N. gonorrhoeae* isolates resistant to spectinomycin and gentamicin, showing that these two antimicrobials are potential treatment options for current cases of therapeutic failure [63]. Similar results for the efficacy of gentamicin were found in a study conducted in China [64]. In isolates of *N. gonorrhoeae* with decreased susceptibility or resistance to extended-spectrum cephalosporins (ESCs), ertapenem was considered effective [65].

It is worth remembering that some of the second-line drugs used to treat gonorrhoea have significant adverse effects, such as fluoroquinolones, which can cause disabling and permanent side-effects in tendons, muscles, joints, and the central and peripheral nervous system [40]. Another second-line drug used is gentamicin, and, although no adverse effects have been reported in the treatment of gonorrhoea, given that the treatment is performed in a single dose [41], it is well reported that aminoglycosides can cause ototoxicity and nephrotoxicity [42].

The control of gonorrhoea is an essential issue in public health, requiring an integrated approach where the provision of effective treatment is essential to interrupt the chain of transmission and reduce the impact of the disease [66]. Knowledge of the sensitivity patterns of this microorganism is essential to establish the best form of treatment. Without this effort, there is a risk that gonorrhoea will become intractable [67–69]. In view of this, the generation and maintenance of national and international programs aimed at control, awareness, and treatment would contribute to a reduction in the incidence and spread of resistant strains of *N. gonorrhoeae*. The ideal would be the creation and implementation of surveillance systems and/or improvement of existing programs, especially in low-income countries, with the objective of collecting epidemiological data on gonorrhoea in each country, region, and/or economic block, since population characteristics can directly influence resistance patterns. In addition, information sharing should be improved at a global level, thus allowing better options for personalised control and treatment to be found [32,70,71].

2.2. Development of New Therapies against N. gonorrhoeae

The development and validation of new drugs require significant time and financial investment, with new antimicrobials often having insufficient efficacy during clinical trials [72]. In addition, research and development of new drugs for the treatment of gonorrhoea and other STIs are relatively scarce when compared to other diseases. By way of comparison, there are 133 studies on gonorrhoea registered on ClinicalTrials.gov,

196 for chlamydia, 86 for syphilis, 44 for trichomoniasis, and 3628 studies for type 1 diabetes mellitus.

There are currently only three molecules with antigonococcal agents at various stages of clinical development, solithromycin, for which a phase III study was recently completed, and gepotidacin and zoliflodacin, which completed a phase II trial.

Solithromycin is a new oral fluoroketolide developed by Cempra, Inc. that targets prokaryotic ribosomes, being active against fastidious Gram-positive and Gram-negative bacteria, including *N. gonorrhoeae*, *C. trachomatis*, and *Mycoplasma genitalium*. Solithromycin is quite active against intracellular bacteria as it has the ability to accumulate in the intracellular medium [73]. The current status of this compound is a phase III trial completed in 2019, where orally administered solithromycin was tested in a noninferiority trial against intramuscular ceftriaxone in combination with oral azithromycin in patients with uncomplicated gonorrhoea [74]. However, the current development status of the drug is unknown as Cempra, Inc has gone through several merger and incorporation processes.

Gepotidacin is a new antibiotic for oral and intravenous use, developed through a public–private partnership between GlaxoSmithKline (GSK), US government's Biomedical Advanced Research and Development Authority, and the Defence Threat Reduction Agency, which acts by inhibiting bacterial topoisomerase type II, of the new triazaacenaphthylene class of antibacterial. Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV via a different mechanism of action from that of quinolones. Gepotidacin is a broad-spectrum antibiotic active against multidrug-resistant bacteria such as MRSA, ESBL-producing Enterobacteriaceae, and *N. gonorrhoeae* [75]. In 2019, GSK started phase III studies, called EAGLE-1 (project BTZ116577) and EAGLE-2 (project 204989), which did not have their data published. However, we believe the findings were promising given that it announced, in March 2022, phase I pharmacokinetic studies in healthy volunteers (ClinicalTrials.gov identifier NCT05271799).

Zoliflodacin is the first representative of a new class of antibiotics called spiropyrimidinetriones, developed by Entasis Therapeutics. Its mechanism of action is through gyrase/topoisomerase II inhibition, with binding sites different from those of fluoroquinolones. It has potent activity against *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, and other atypical bacteria [76]. Currently, phase III clinical trials with zoliflodacin have been carried out in a partnership between Entasis with the Global Antibiotic Research and Development Partnership (GARDP) (ClinicalTrials.gov identifier NCT03959527).

3. Conclusions

The treatment of gonorrhoea, as well as other STIs, has been a challenge, since its spread has been favoured due to the increase in unprotected sex. In addition, the indiscriminate use of antibiotics during the COVID-19 pandemic has raised concerns about increasing selective pressure on *N. gonorrhoeae*, which may contribute to the rapid emergence and spread of resistant strains of bacteria. Therefore, a joint effort between public and private initiatives is essential for the search and development of new antibiotics. In addition to more investments in medical education, since STIs are preventable diseases, investments in educational campaigns are necessary to raise awareness among the general population.

Author Contributions: Conceptualization, O.N.S. and J.L.R.M..; writing—original draft preparation, O.N.S.; writing—review and editing, J.L.R.M., E.M.H.P., S.A.O., O.N.S. and F.A.C.G.; visualization, J.L.R.M.; supervision, O.N.S.; project administration, O.N.S. and J.L.R.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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