Artigo de Revisão

Gonorreia: Resistência aos Antimicrobianos e Novos Fármacos

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RESUMO – O impacto global das infeções sexualmente transmissívies continua a ser elevado, com significativa morbilidade e mortalidade associadas. A gonorreia é a segunda infeção sexualmente transmissível mais notificada na Europa, sendo que a sua incidência tem vindo a aumentar nos últimos anos. Apesar de tradicionalmente considerada uma infeção curável, a resistência da *Neisseria gonorrhoeae* aos antimicrobianos já se estende na atualidade aos macrólidos, tetraciclinas, combinações de sulfonamidas e trimetropim, quinolonas, e até mesmo ceflosporinas. Estes elevados níveis de resistência aos antimicrobianos podem colocar um dos maiores desafios às estratégias de prevenção e controlo das infeções sexualmente transmissíveis, ao permitirem a ocorrência de infeções não tratáveis no futuro. Deste modo, o desenvolvimento de novos antimicrobianos e/ou de novas combinações terapêuticas é uma necessidade urgente. Neste artigo é revista a evolução das resistências da *Neisseria gonorrhoeae* aos antimicrobianos ao longo dos anos, assim como os novos fármacos em desenvolvimento para o tratamento desta infeção.
PALAVRAS-CHAVE – Antibacterianos; Doenças Bacterianas Sexualmente Transmissíveis/tratamento; Farmacorresistência Bacteriana; Gonorreia/tratamento; Neisseria gonorrhoeae/efeito dos medicamentos.

Gonorrhea: Antimicrobial Resistance and New Drugs

ABSTRACT – *The global burden of sexually transmitted infections remains high, with significant associated morbidity and mortality. Gonorrhea is the second most notified sexually transmitted infection in Europe, and its incidence has been increasing in the last years. Although traditionally considered a treatable infection, antimicrobial resistance of Neisseria gonorrhoeaeincludes at present also macrolides, tetracyclines, sulfonamides and trimethoprim combinations, quinolones, and even cephalosporins. These high levels of gonococcal resistance to antimicrobials resulting in untreatable infections in the future may become one of the greatest challenges to the prevention and control of sexually transmitted infections, which may be a significant major public health issue. Therefore, the development of novel antimicrobials and/or new dual antimicrobial therapy regimens is urgently needed. In this paper, evolution of antimicrobial resistance of Neisseria gonorrhoeae is reviewed, along with new drugs currently under development for the treatment of this infection.*
KEYWORDS – *Bacterial Agents; Drug Resistance, Bacterial; Gonorrhea/drug therapy; Neisseria gonorrhoeae/drug effects; Sexually Transmitted Diseases, Bacterial/drug therapy.*

1. BACKGROUND

The global burden of sexually transmitted infections (STIs) remains high, with more than 1 million curable STIs occurring each day.[1] Worldwide, morbidity and mortality resulting from STIs compromise not only quality of life but also sexual, reproductive health and newborn health.[2] STIs also indirectly facilitate sexual transmission of HIV (by two to five times, in some populations) and cause cellular changes that precede some cancers. Left untreated, STIs can lead to severe complications and sequelae in both men and women, including pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal death and congenital infections.[1] Therefore, STIs impose a substantial strain on the budgets of national health systems and negatively impact the overall well-being of individuals by their physical, psychological and social consequences.[2] Although the

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numbers of men and women infected with STIs are similar, complications disproportionately affect women in several ways.[2,3]

Gonorrhea, with 89 239 cases reported in 2017, is the second most notified STI in Europe, only surpassed by chlamydia. Incidence of *Neisseria gonorrhoeae* infection in Europe has also been increasing in the last years (from 8.2 per 100 000 population in 2008 to 23 per 100 000 population in 2017).[3] This increase is more pronounced among men, who have consistently higher rates of infection then women, and is mostly driven by increasing cases in men who have sex with men (MSM). This rising tendency is probably related with increased risk behaviors, in some cases linked to changing sexual practices with the use of HIV pre-exposure prophylaxis[4], increased testing among MSM (particularly at extra-genital sites such as the oropharynx) and the more widespread use of nucleic acid amplification tests. In Portugal, incidence of gonorrhea is also increasing (16% increase in 2017 comparing to 2016), with an average of 3.8 cases per 100 000 inhabitants in 2017.[5]

These consistently high rates of gonorrhea in Europe are of particular concern if one considers the high levels of resistance to antimicrobial agents, which threaten the currently recommended treatments and continue to be a challenge in STI prevention and control efforts.[3] As there is no gonococcal vaccine, disease control relies entirely on prevention, diagnosis, and, most importantly, antimicrobial therapy.[6]

2. ANTIMICROBIAL RESISTANCE IN NG

N. gonorrhoeae is a common and preventable causative agent of ureteral discharge. Although considered a treatable infection, high levels of gonococcal resistance to antimicrobials may pose one of the greatest challenges to STIs prevention and control, by resulting in untreatable infections in the future, causing a significant major public health problem.[1] In fact, over the past decades, *N. gonorrhoeae* has developed resistance to almost all medicines used to treat this infection, raising the possibility of untreatable gonococcal infections.[2]

Antimicrobial resistance of *N. gonorrhoeae* appeared shortly after the introduction of antimicrobials, at the beginning of the 20th century (Fig. 1). Factors contributing to increasing resistance include suboptimal diagnosis and surveillance capacity, easy availability of antimicrobials (including counterfeit drugs) and lack of drug quality control. Moreover, *N. gonorrhoeae* is able to exchange DNA, especially in the pharynx, to maintain resistance genes on the chromosome, and to induce antigenic variations that permit an escape from the immune system. Together, these facts contributed to the rapid development of resistance.[1]

In 2019, resistance has extended to macrolides (including azithromycin), tetracyclines, sulfonamides and trimethoprim combinations and quinolones. More recently, countries with good quality surveillance have also demonstrated increased resistance to cephalosporins including cefixime and ceftriaxone, the "last line" of treatment. Indeed, 10 countries have reported treatment failure with extended-spectrum (third-generation) cephalosporins.[1] This is particularly troublesome as extended-spectrum cephalosporins are currently the last remaining options for effective empiric first-line antimicrobial monotherapy in Europe.[7]

According to the WHO, first-line antimicrobial therapy must be highly effective, widely available and affordable, lack toxicity, comprise a single dose, and rapidly cure at least >95% of infected patients.[6] Due to the observed decrease in susceptibility to antimicrobials in the past years,[5] European treatment guidelines now recommend combination treatment with ceftriaxone plus azithromycin as first-line therapy, in order to reduce the development and/or spread of resistance to these antimicrobials.[7]

3. GONOCOCCAL ANTIMICROBIAL SURVEILLANCE PROGRAMME (GASP)

Monitoring the susceptibility patterns of *N. gonorrhoeae* is essential for detecting and tracking emerging resistance and for adjusting treatment recommendations. Since 1992, countries monitor the emergence of resistant strains of *N. gonorrhoeae* through "Gonococcal Antimicrobial Surveillance Programme" (GASP), a global laboratory network now including more than 60 countries. GASP monitors patterns of resistance and provides data to develop treatment guidelines. This surveillance program monitors the longitudinal trends in antimicrobial resistance (AMR) and provides data to inform treatment guidelines.

European countries account for the nearly half (46%) of the reporting countries in 2016. Participation in GASP is much lower among countries in the African region, although it has increased over the past few years. Despite this progress, the full magnitude of the problem of gonococcal AMR remains unknown due to a lack of data in many countries. This lack of information is particularly troublesome in countries with the highest gonorrhea burden and thus the greatest need for AMR monitoring.[1]

Since 2009, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP), coordinated by the European Centre for Disease Prevention and Control (ECDC), aims at performing a surveillance of the susceptibility to antimicrobial agents, in order to ensure effective patient management and monitor current and emerging trends in antimicrobial resistance in Europe.[5]

4. RESISTANCE TO TRADITIONAL ANTIMICROBIALS

4.1. Cephalosporins

Cefixime is one of the antimicrobials commonly used for the treatment of gonorrhea. Resistance to this agent has remained stable at around 2% since 2014, and there have been no significant changes in cefixime minimum inhibitory concentration (MIC) distribution in the last few years. Cefixime resistance seems to be significantly associated with isolates from heterosexual males compared to MSM, females compared to males, and genital isolates compared

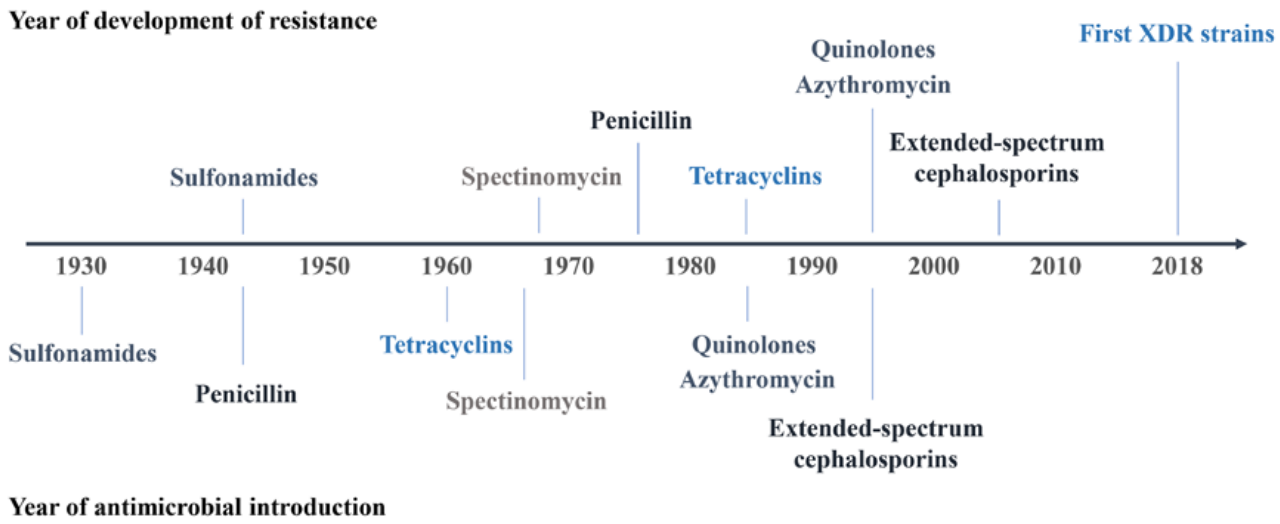

Figure 1 - Introduction of new antimicrobials and subsequent development of resistances (XDR stands for extensively drug resistant).

to anorectal isolates. Pharyngeal isolates in general have significantly higher cefixime MICs (0.125-0.25 mg/L) than anorectal and other isolates.

Ceftriaxone is another third-generation cephalosporin used in the treatment of this infection. Resistance to this antimicrobial is rare and seems to be decreasing, with seven isolates in 2013, five in 2014, one in 2015 and none in 2016 and 2017. Moreover, the MIC distribution for ceftriaxone in 2017 shows a significantly higher proportion of more susceptible gonococcal isolates (MIC ≤0.016 mg/L) compared with the previous year, again arguing in favor of more susceptible isolates.[5]

Considering global data, 30% of the included countries report that >5% of specimens have decreased susceptibility to extended spectrum cephalosporins (ceftriaxone and/or cefixime). This problem is of particular magnitude in Asian countries such as Japan, South Korea, and Taiwan.

4.2 Macrolides

Azithromycin is now recommended as first-line therapy for gonorrhea, in combination with ceftriaxone. Resistance to this agent has remained stable since 2014, at levels around 7%-8% (7.5% in 2017). The MIC distribution for azithromycin also seems to be stable comparing to previous years, with most resistant isolates showing a MIC just above the breakpoint (MIC >0.5 mg/L). However, it is important to note that high-level resistance to azithromycin has been recognized, with seven cases isolated in 2016 and another seven in 2017. These seven isolates include one from Portugal, three from Norway, two from the United Kingdom and one from Finland. Azithromycin resistance seems to be highest in isolates from MSM (8.3%), followed by heterosexual males (7.2%), and lowest in females (6.8%). Moreover, azithromycin resistance seems to be significantly associated with isolates from those under 25 years of age compared to those over 25 years of age.[5]

Considering global data, nearly half (49%) of the included countries report that >5% of specimens have decreased susceptibility to azithromycin.

4.3. Quinolones

Ciprofloxacin is not recommended as first line therapy for gonorrhea. In fact, resistance levels to this antimicrobial remain high (46.5% in 2017), similarly to previous years. Resistance seems to be higher in heterosexual males (51.1%) comparing to MSM (41.1%), in those over 25 years old comparing to those under 25 years old and in the absence of a concurrent chlamydial infection. Moreover, ciprofloxacin resistance is significantly associated with genital and pharyngeal infection sites comparing to anorectal isolates.[5]

Considering global data, 95% of the included countries report that >5% of specimens have decreased susceptibility to ciprofloxacin, with 17% of countries revealing >90% of resistant strains.

5. THE PROBLEM OF EXTENSIVELY DRUG-RESISTANT STRAINS

The increase in *N. gonorrhoeae* antimicrobial resistance worldwide can potentially lead to a pandemic of extensively drug-resistant (XDR) strains, with serious public health consequences. XDR strains are defined as those resistant to two or more of the antibiotic classes currently recommended for the treatment of gonorrhea, or three or more of the less frequently used antibiotic classes.

XDR strains of *N. gonorrhoeae* have been detected in multiple regions, and a large proportion of the circulating strains worldwide are very close to transform into XDR strains.[8] To prevent the emergence of drug resistant strains,

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Table 1 - New antimicrobials undergoing evaluation for treatment of gonorrhea and summary of their mechanism of action.

ANTIMICROBIAL	CLASS	MECHANISM OF ACTION
Solithromycin	Broad-spectrum oral fluoroketolide	Inhibits bacterial translation by binding to three prokaryotic ribosomal sites of 23S ribosomal RNA
Zoliflodacin	Hydroquinoline	Inhibits the spiropyrimidinetrione topoisomerase (type II)
Gepotidacin	Triazacenaphthylene	Inhibits bacterial DNA replication through a unique interaction on the bacterial subunits of DNA gyrase (GyrA) and topoisomerase IV (ParC)
Lefamulin	Semi-synthetic pleuromutilin	Inhibits protein synthesis by binding to the peptidyl transferase center of the 50S bacterial ribosome, thus preventing the binding of transfer RNA
Aminoethyl spectinomycins	Semi-synthetic analogs of spectinomycin	Inhibits protein synthesis by binding to the 30S ribosomal subunit

WHO now recommends dual therapy with ceftriaxone plus azithromycin.[1]

6. NEW DRUGS IN PERSPECTIVE

As the emergence of drug resistance seems to be unstoppable, new treatment options are necessary in order to control gonorrhea. One possible approach is to assess whether older drugs, such as gentamicin and spectinomycin, may be used in novel combinations for treatment of gonorrhea.[9] Another option is the development of new antimicrobials.[6]

6.1. Already Existing Antimicrobials

Sitafloxacin is a new-generation broad spectrum fluoroquinolone, mostly used for respiratory infections. According to recent studies, it seems to be a good candidate to be included in dual antimicrobial therapy for gonorrhea, particularly in cases of cephalosporin resistance or allergy. Delafloxacin is another fluoroquinolone currently being studied for the treatment of gonorrhea, although more studies are required to correlate its promising in vitro results with clinical treatment outcomes. Novel combinations of previously existing antimicrobials have also been tested in recent studies, with five of them showing promise in the treatment of gonorrhea. These include gentamicin + ertapenem, moxifloxacin + ertapenem, spectinomycin + ertapenem, azithromycin + moxifloxacin, and cefixime + gentamicin. Gentamicin is an aminoglycoside already included in several guidelines in combination with azithromycin, as an alternative treatment when first-line therapies fail. Recently, gentamicin has shown promise when used in combination with ertapenem or cefixime, with high levels of efficacy and synergism.[6]

6.2. New Antimicrobials

Ideally, new antimicrobials should belong to antibacterial families different to the ones already included in treatment guidelines, in order to delay the appearance of resistances as much as possible (Table 1). Currently, only three molecules in this category have reached clinical trials: solithromycin, zoliflodacin, and gepotidacin.[6]

Solithromycin is a broad-spectrum oral fluoroketolide which targets three prokaryotic ribosomal sites.[10] *In vitro* studies have demonstrated promising results, with more activity against *N. gonorrhoeae* than the antimicrobials currently recommended for its treatment. Phase II clinical trials were concluded with 100% efficacy in the treatment of men and women in all studied sites (genital, oral, and rectal).[10] The drug is currently in phase III trials.[6]

Zoliflodacin has a novel mechanism of action, by inhibiting the spiropyrimidinetrione topoisomerase. Early in vitro studies showed promising results, with the compound being highly effective against isolates from 21 European countries.[11] Zoliflodacin also did not present any cross-resistance to other antimicrobials.[11,12]

Finally, gepotidacin is a novel triazacenaphthylene antibacterial which inhibits bacterial DNA gyrase and topoisomerase IV via a unique mechanism. The compound showed no antagonism when combined with levofloxacin, azithromycin, tetracycline, and ceftriaxone; the combination of gepotidacin with moxifloxacin had a synergistic effect. This drug underwent a phase II evaluation, showing that oral gepotidacin was more than 95% effective in treating uncomplicated urogenital gonorrhea.[13]

Apart from these three drugs in clinical trials, other compounds are still in early experimental phases. This is the case of lefamulin, a novel semi-synthetic pleuromutilin that has showed potent activity against gonococcal isolates and no significant cross-resistance to other antimicrobials. Furthermore, this compound has also proved to be active against other relevant bacterial pathogens causing STIs, namely *Chlamydia trachomatis* and *Mycoplasma genitalium*.[14]

Aminoethyl spectinomycins belong to a new class of semisynthetic analogs of the antibiotic spectinomycin, currently being studied for the treatment of drug-resistant gonococci.

Although more studies are needed, they seem a promising alternative for spectinomycin and antibiotics such as ceftriaxone against drug-resistant gonorrhea.[15] As with lefamulin, these agents also seem to be active against other relevant bacterial pathogens in STIs, such as *Chlamydia trachomatis* and *Mycoplasma genitalium*.

7. PUBLIC HEALTH IMPLICATIONS AND FUTURE STRATEGIES

In order to achieve the goal of controlling sexually transmitted infection epidemics as a public health concern, several targets have been defined by the WHO. These include that, by 2020, 70% of countries report on antimicrobial resistance in N. gonorrhoeae, and that, by 2030, the incidence of infections with *N. gonorrhoeae* would have fallen by 90% globally.[2]

To achieve this goal, a critical component of the Global STI Strategy is strengthening STI surveillance and program monitoring systems.[1] There is an urgent need to strengthen prevention activities aimed at increase testing in individuals at highest risk. This could be achieved by targeting specific risk groups with evidence-based messages and methods. Social media and apps should be considered for prevention campaigns in addition to traditional approaches.[3] Overall, stronger surveillance is needed to better characterize the extent of antimicrobial resistance among gonococcal strains.

The potential impact of the introduction of pre-exposure prophylaxis of HIV infection in different communities should also be monitored, including through the surveillance of STIs, sexual behaviors and drug resistance. The increasing use of DNA amplification assays should also be viewed with caution, as it does not allow yet traditional antimicrobial susceptibility testing.

CONCLUSION

The continuing low cephalosporin resistance in Europe is promising, considering that these are the last remaining options for empiric first-line monotherapy. Monitoring is nevertheless needed as XDR strains from Southeast Asia can be imported through migration and sexual tourism. Due to the high levels of documented resistance, neither azithromycin nor ciprofloxacin are currently recommended for gonorrhea monotherapy, unless the isolates are first shown to be susceptible.

In previous years, there has been a tendency for MSM to have a lower risk of harboring antimicrobial resistant isolates,[16] which is concordant with a lower risk of antimicrobial resistance among anorectal isolates.

Although European overall resistance levels seem to be stable for all antimicrobials, the response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe,[17] which is currently under revision, should continue to be observed to help identify and report treatment failures and ensure that gonorrhea remains a treatable infection. In addition, the development of novel antimicrobials and/or new dual antimicrobial therapy regimens is urgently needed.

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