

Neisseria Gonorrhoeae Infections: Biological Diagnosis, Antibiotic Resistance and Treatment

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Abstract

Neisseria gonorrhoeae is a Gram-negative diplococcus in coffee beans, specific to the human genital tract. This bacterium is, along with *Chlamydiae trachomatis*, one of the main germs responsible for sexually transmitted infections in the world. Infection with *Neisseria gonorrhoeae* is associated with a wide range of noisier clinical manifestations in humans. It is also responsible for several complications and sequelae affecting the reproductive pathways, especially in women. In recent years, the incidence of *Neisseria gonorrhoeae* infections has increased, as has its resistance profile to the different classes of antibiotics available.

Hence the interest in presenting an overview of the literature's data on microbiological diagnosis of *Neisseria gonorrhoeae* and its various pathogenic mechanisms as well as antibiotic resistance mechanisms.

Keywords: *Neisseria Gonorrhoeae*; *Chlamydiae Trachomatis*

Introduction

Neisseria gonorrhoeae (gonococcus) is a bacterium in the form of gram-negative and strict aerobic diplococcus. This very fragile pathogen is specific to the mucous membranes of the human genital tract. Its transmission is essentially through direct sexual transmission [1]. In addition, *Neisseria gonorrhoeae* is, along with *chlamydiae trachomatis*, one of the main germs responsible for sexually transmitted infections worldwide [2,3]. While the symptomatology generated in men is often noisy, it is in more than 50% of cases mute in women promoting dissemination and at the same time constituting a major reservoir of infection [4].

Over the past decade, the incidence of *Neisseria gonorrhoeae* infection has increased, particularly among the young population [5]. According to the World Health Organization (WHO), the incidence of gonococcal disease has increased by 21% since 2005 and estimates 78 million new cases of gonorrhoea per year. Estimates of prevalence and incidence varied by region and gender [6]. In Africa, the incidence of Gonococcal infection in symptomatic subjects was estimated at 8.2 million new cases per year. In Morocco,

gonococcal disease is responsible for 62.8% of urethral discharges, making it the most common cause of sexually transmitted infections [7]. For example, infections with *Neisseria gonorrhoeae*, or gonococcal disease, are a public health problem, both in their high morbidity and in their socio-economic impact [6]. In addition, the emergence of resistance to multiple classes of antibiotics (penicillins, tetracyclines, fluoroquinolones and currently third-generation cephalosporins) represents an obstacle to controlling this infection [8,9,10]. Bacteriological diagnosis is based on conventional identification methods namely direct examination after Gram coloring, culture on special environments associated with the study of antibiotic sensitivity, and more recently techniques gene amplification [11].

Pathophysiology

N. gonorrhoeae is a mandatory human pathogen, as its pathogenic progress (transmission, adhesion, colonization and invasion), the bacterium expresses many virulence factors to promote survival and replication while remaining invasive and able to avoid immune responses to promote replication and survival.

Gonococcus's adhesion, survival and multiplication capabilities have been attributed to some of its elements that appear to be involved in its virulence. Thus, *Neisseria gonorrhoeae* adheres to the microvillousities of epithelial cells thanks to its adhesins. Among them are mainly: porins, the main proteins of external membranes, the Opa proteins (opacity associated proteins) represented by Opa₅₀ which adheres to heparin sulphate of proteoglycans (HSPGs) and Opa₅₂ that attach specifically to CEACAMs (carcinoembryonic antigen related cell adhesion molecules) and lipo-oligosaccharide (LOS), a major glycopeptide of the outer membrane of gonococcus [12,14]. Type IV pili are also found, which, thanks to the phenomena of "twitching" and glycosylation [15,16,17], confer a form of motility on the bacterium and allow it to surface exploration and attachment to epithelial cells mainly at the level of different mucous membranes and strengthen the adhesion of the bacterium [17,18]. *Neisseria gonorrhoeae* endocytosis within vacuoles multiplies, then is released by exocytosis into the connective tissue under epithelial and this after fusing with the basal membrane [19]. Several mechanisms allow Gonococcus to escape the immune response. Notably, the synthesis of IgA proteases that allows *Neisseria gonorrhoeae* to cleave these antibodies as well as the outer membrane that prevents the lytic action of lysozyme [20,21]. In addition, lip oligosaccharides (LOS) are capable of producing toxic effects by stimulating the production of TNF (Tumor Necrosis Factor) by macrophages at the sub-space causing damage to the mucous cells.

In women, the predominance of lactobacilli within the normal vaginal flora ensures the ecological balance of the vagina, notably by hydrolyzing glycogen in lactic acid which contributes to the acidification of the pH and by the secretion of hydrogen peroxide, inhibiting most pathogens including *Neisseria gonorrhoeae*. This explains the predisposition of women with unbalanced vaginal flora to develop gonococcal disease in the event of exposure. Furthermore, the presence of the complement receptor (CR3) in the endocol and exocol may partly explain the asymptomatic form in women. Indeed, the endocytosis mediated by CR3 via the inactivated C3B on the surface of the gonococcus causes an internalization of the bacterium in the cells of the cervical epithelium and its elimination, without influx of neutrophils, therefore infection most often unnoticed. The absence of CR3 expression in human urethral epithelium contributes to the noisy nature of these infections [1,23]. Finally, it is necessary to mention the difficulties

encountered in the development of a specific vaccine against *Neisseria gonorrhoeae*; and which are related to the different surface modulations and one-off mutations experienced by its various surface antigens [24,25].

Clinic

In men, genital gonococcal infection most often manifests itself in acute urethritis, which occurs after a contagious and silent incubation period of 2 to 7 days [2,18]. The symptomatology is noisy characterized by purulent urethral discharge, painful dysuria and intense urination burns [26,27]. Symptoms of inflammatory mastitis, or even balanitis, can also be found. Locoregional complications may occur. It is mainly orchitis-epidymitis. In women, gonococcal infection is asymptomatic in 70 - 80% of cases. The most common manifestation is cervicitis. Anamnesis may find a notion of purulent leukorrhoea, pelvic gravity and/or associated signs of urethritis. Examination most often shows a non- or little-inflammatory cervix with a purulent flow to the cervical opening [2]. Complications are more numerous than in humans: endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis with reproductive sequelae in lack of treatment, (infertility, ectopic pregnancy, pelvic pain) [28,29]. In both sexes, infectious outbreaks can be found in extra genital, including anal, pharyngeal and conjunctival. Scattered forms can also be observed especially in women in the form of sepsis, eye damage or even other locations (articular, skin, heart, meningeal) [27,30].

Biological diagnosis

The diagnosis of infections with *Neisseria gonorrhoeae* relies primarily on direct methods (direct examination, culture, molecular biology), which are based on the detection of gonococci or their genomes in the various sites accessible for sampling (urethra, cervix, vagina, rectum, pharynx, and urine).

Taking

The latter, more or less invasive, differs according to sex, symptomatology, location and techniques used as summarized in table 1 [2,32,33]. It is important that the sample is taken before any antibiotic therapy and according to an optimal procedure, in order to improve the reliability of the diagnosis. Thus, the experienced practitioner should be attentive to certain principles when taking the sample; these are summarized in table 2 [34]. Gonococcus is a fragile bacterium that tends to self-lyse and does not survive desiccation and temperature variations. Therefore, the use of a suit-

able environment when transporting samples seemed necessary (e.g. Vandekerkovemedium) [35].

Clinical form	Types of samples
Vaginal attack Screening in women	Vaginal swab Auto-vaginal swab
Suspicion of endocervicitis	Removal of the endocol bysecremage - collection of urine (first jet)
Suspicion of urethritis in humans	Remote urethral sampling of a urination with two dacron swabs (direct examination/culture) after cleaning the pipe-/- collection of urine (first spray)
Suspicion of an ano-rectal location	Ano-rectal sampling after cleaning the anal opening
Other locations	Pharyngeal, ocular, skin, joint fluid, hemocultures.

Table 1: Different Types of Samples Taken by Location and Sex NF,QBDN,IGH [2.32, 333].

Prélèvement	Msures to take
Urine sample	Warning: Gene amplification diagnosis based on a urine sample is less sensitive in women than a cervical or vaginal smear. Sample collection at least one hour after last urination Take the first urine stream (unlike the test for the diagnosis of urinary tract infection, for which medium-jet urine is more appropriate). In practical terms: the patient must collect the first drops of urine and fill the container up to a maximum of 20 ml.
Cervical smear	Before sampling, remove any cervical secretions with a large swab. Insert the swab into the cervix sufficiently (1-2cm) and rub the cervical wall in a rotating motion (at least 2 rotations). Avoid contact with the vaginal wall when removing the swab
Pharynx smears	Apply sufficient pressure when taking Carefully remove: not only rub the posterior wall of the pharynx but also the two tonsils
Anal smear	Do not use lubricant or local anesthesia. Insert the swab sufficiently in a rotating motion (3-5cm-the cotton-covered end should not be visible). In a delicate rotating motion and pressing lightly, rub the wall for 30 seconds to promote the absorption of gonococcus in the swab.

Table 2: Steps to Take for An Opitmal Sample to Diagnose Gonorrhea [34] (GNR).

Direct review

It is made on a spread of urethral flow, colored with Gram or failing methylene blue [28]. Gram-negative diplococs are set in intracellular "coffee beans"(Figure 1). This test has a sensitivity and specificity greater than 95% in cases of symptomatic male urethritis. However, it is more difficult in women vaginal or endocervical secretions of up to 65% as well as on other types of pre-lifts (pharynx, rectum). Therefore, a confirmation by culture is required [2,28.36,37].

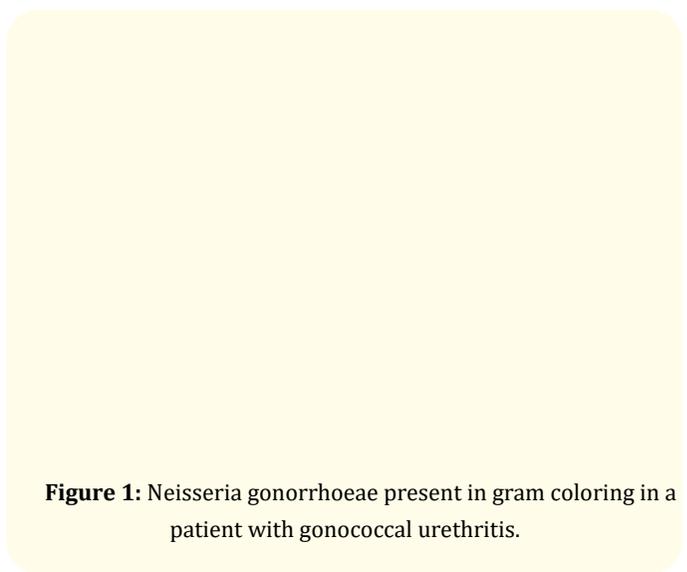


Figure 1: Neisseria gonorrhoeae present in gram coloring in a patient with gonococcal urethritis.

Isolation and identification

The cultivation of *Neisseria gonorrhoeae* is difficult, due to its fragility, and these multiple metabolic requirements [5,37]. Thus, in addition to the need for an optimal growth temperature of 36 - 37°C and a moist atmosphere enriched with CO₂ (5 - 10%), its cultivation requires a cooked blood agar or supplemented "chocolate agar" (hemine, blood or starch) to avoid the toxicity of fatty acids in agar [38]. In addition, other compounds will need to be added after sterilization including iron and cupteine (Polyvitex, glucose supplement), as well as antibiotics (Vancomycin, C olimycin, nyastatin, and other antifungal agents) to inhibit the growth of certain bacteria that can hinder the growth of *Neisseria gonorrhoeae* [39].

The orientation of bacteriological diagnosis must be accompanied by a macroscopic examination of the colonies; which appear in 18 - 48 hours, greyish, smooth, with regular edges, 0.5 - 1mm in diameter; followed by confirmation by microscopic examination [38,40]. Colonies are positive oxidation, positive catalase. The different biochemical characteristics of gonococcus, including the absence of maltose oxidation, are defined when identified on Api NH galleries [40]. Culture is the standard gold for diagnosing Infection

with *Neisseria gonorrhoeae*. Indeed, in addition to bacteriological identification, it is the only method to test the susceptibility of strains to antibiotics. It also allows, to carry out complementary tests such as serotyping and genotyping essential for epidemiological follow-up [5,40]. Moreover, it has a sensitivity approaching 90% and a specificity of almost 100% for the removals of the urethra and cervix. However, there are some drawbacks to cultivation, including the need to keep microorganisms viable, the difficulty of growing certain samples, and the time to obtain results [41,1].

Molecular biology

Molecular biology methods detect nucleic acids in the bacterial genome by direct molecular hybridization using DNA probe or after in vitro amplification (NAATs- *Nucleic Acid Amplification Tests*) [5]. Currently, existing gene amplification techniques, known as second generation, are more specific than this first-generation ones. Indeed, the latter were the object of cross-reaction with the *Commensales Neisseria*, responsible of false positives [41]. These improved techniques have, as a result, become more sensitive and more suited to the series compared to the culture. They are also suitable for all sampling sites including the first urine jets and vaginal self-samples. Most NAATs on the market are called "multiplex", allowing early diagnosis by simultaneous evidence of *Chlamydiae trachomatis* and *Neisseria gonorrhoeae*, or more than two sexually transmitted infection agents [42,43]. However, the gene amplification technique only provides the diagnosis of gonorrhoea. Thus, it seemed necessary to clarify that only the culture supplemented by the realization of an antibiotic bigram allows the identification of antibiotic resistance, and at the same time, the rectification of an inadequate treatment [11].

Antibiotic sensitivity

The minimum inhibitory concentrations (MICs) of the different antibiotics can be measured in the laboratory for clinical strains, if they could be isolated [11]. Antibiotics currently recommended by the French Microbiology Biopath Antibiotic Committee CA-SFM/EUCAST in the standard list for *Neisseria's* antibiotic *gonorrhoeae* are penicillin G, cefixime, ceftriaxone, spectinomycin, has azithromycin and ciprofloxacin. The additional list includes chloramphenicol and tetracyclines [45]. The method of diffusion on cooked blood agar (plus vitamin supplements) using discs loaded with antibiotics gives random results with, in particular, a great difficulty in differentiating fully sensitive strains from intermediate sensitivity strains for many families of antibiotics [46]. In case of insuffi-

cient growth after 24 hours, extend the incubation by an additional 20 hours. The production of beta-lactamase must be detected by a chromogenic technique as soon as it is isolated. It confers resistance to penicillin G, amino-, carboxyethyl ureido-penicillin's. The determination of MICs by the agar dilution method remains the reference method, with the detection of reduced sensitivity to penicillin's will be performed routinely by determining the CMI of penicillin G (CMI - 0.06mg/L). Indeed, it also makes it possible to carry out a routine evaluation of The CMI for the main molecules used in therapeutics (ceftriaxone: CMI - 0.125mg/L, Cefixime: CMI - 0.125 mg/L and ciprofloxacin: 0.03 mg/L). The decrease in sensitivity to 3rd generation cephalosporins is best detected with cefixime [45,46].

Antibiotic resistance

Natural antibiotic resistance of *Neisseria gonorrhoeae*

Neisseria gonorrhoeae is a species naturally resistant to trimethoprim, colistin, and glycopeptides. These natural resistances are used to define antibiotic supplements used in selective settings.

Evolution of acquired resistance

Sulfonamides were one of the first classes of antibiotics to be widely used in the treatment of *Neisseria gonorrhoeae* infections, although this was for a short time, given the rapid onset of resistance [47]. During the 1940s, penicillin became the mainstay of gonococcal treatment. However, an increase in minimal inhibitory concentrations of penicillin and cyclins (considered a therapeutic alternative) to *Neisseria gonorrhoeae* caused their prescription to be discontinued in the late 1980s. This period also saw the advent of third-generation cephalosporins and quinolones as the main molecules prescribed in the treatment of gonococcal disease. The latter rapidly developed resistance [49]. Third-generation cephalosporins then became first-line antibiotics. Nevertheless, a decrease in sensitivity to cephalosporins has begun to appear among the strains of *Neisseria gonorrhoeae*. Between 1999 and 2002, the percentage of *Neisseria gonorrhoeae* isolates with a minimum cefixime inhibitor concentration of 0.5g/ml or more increased from 0% to 30% in Japan [47]. Other documented cases have been reported in Hong Kong and South Korea [50,51]. In July 2011, Ohnishi, *et al.* reported the case of a strain of *Neisseria gonorrhoeae* H041, isolated at the pharyngeal level in a prostitute, wearing a new *PenA* mosaic allele, which confers resistance to ceftriaxone and cefixime with MICs 8 to 16 times more than the usual MICs (between 2-4g/ml) [11].

Clinical responses correlated with the decrease in cephalosporin SJs are still little known. Nevertheless, therapeutic failures of cefixime in people infected with less sensitive *Neisseria gonorrhoeae* isolates have been reported. The first failure appeared in Japan 2003, in patients treated with multiple doses of cefixime 200 mg against *Neisseria gonorrhoeae* isolates with CMI of 0.125g/l-1g/l. The response of the Japanese authorities was swift with a transition to ceftriaxone as the first line of treatment in 2006. In 2010, the first two cases of cefixime resistance in Europe were reported in two heterosexual Norwegian men. Both had presented a therapeutic failure in the face of 400mg doses of cefixime, but responded well when administering a 500 mg dose of intramuscular ceftriaxone [52]. There is currently no clear evidence of clinical resistance to ceftriaxone, although it is to be feared given the increase in minimal inhibitory concentrations [11].

In Canada, *Neisseria gonorrhoeae's* azithromycin resistance is an established fact and it spreads above 5% [52]. In the United Kingdom, the spread of a clone of high-level azithromycin-resistant *Neisseria gonorrhoeae* [53].

Resistance mechanisms

The acquired resistances of *Neisseria gonorrhoeae* follow the accumulation of chromosomal mutations or genetic transfers. The acquisition of nude DNA is fostered by the natural processing capacity of this species. Genetic material from other strains of *Neisseria gonorrhoeae* or strains of bacterial commensal flora can be integrated by homologous recombination into the chromosome of *Neisseria gonorrhoeae*. This mechanism mainly concerns changes in the penicillin binding protein gene at which fragments of exogenous DNA have been integrated, creating real mosaic genes encoding penicillin binding proteins. decreased affinity for penicillin's. The acquisition of TEM1 penicillinase of plasmid origin has also been described [55]. Cyclone resistance is related to the transfer of the *tetM* gene, initially described in streptococci and carried by a transposon located at *Neisseria gonorrhoeae* on large plasmids conjugative [56]. The protein *tetM* encoded by the *tetM* gene protects the ribosomal target from the action of the cyclones. Chromosomal resistances were also implicated. They are related to alteration of major pi porin, hyperexpression of the Mtr CDE efflux pump, or changes in targets, such as the mutation of the *rpsJ* gene encoding ribosomal protein S10 [47]. For quinolones, single or combined mutations of genes encoding type II topoisomerases plays a major role in resistance. Notably, those of the *gyrA* gene

encoding subunit A of gyrase DNA (theS91 and D95 mutations), and then the Gene byC encoding for subunit C topoisomerase IV. The hyperexpression of the Mtr CDE efflux system plays only an incidental role [47,57,58]. Decreased sensitivity to third-generation cephalosporins involves several mechanisms, including :47:

- Mutations in *penA*, *penC*, *ponA* genes, responsible for alteration of penicillin-binding proteins (PBP1 and/or PBP2)
- Mutations in the *penB* gene responsible for a major PI porin modification
- Hyperexpression of the MtrC-MtrD-MtrE efflux system, related to mutations in the *mtrRD* codant genea *mtr* CDE operon repressor or mutations in the *mtrR* promoter

For macrolides, it was found that the number of alleles of the 23S gene of RNA with mutations C2611T or A2059G was strongly correlated with resistance to azithromycin and mutation at the position of the amino acid G45 in the MtrR protein independently predicts resistance to azithromycin [57].

Treatment

Ideally the recommended therapeutic regimen, on the front line, should be able to treat 95% of infections with *Neisseria gonorrhoeae*. Furthermore, the recommended antibiotic therapy, should be highly effective, widely available, and affordable in quantity and in appropriate dose, it should also be devoid of toxic effect, with the possibility of single dose administration. Other criteria, such as prevalence, local epidemiology, frequency of transmission, treatment strategy, cost and diagnostic tests, should be considered in the event of a decision to modify the recommended treatment [62,63]. In response to the increase in antibiotic resistance experienced by *Neisseria gonorrhoeae*, it has been recommended to use a combination of antibiotics. The choice of molecules varies by population and site of infection (Table 3) [61,62]. New forms of biotherapy have also been evaluated for the treatment of uncomplicated forms of urogenital gonococcal disease. These are 240 mg gentamicin in single intramuscular (IM) and azithromycin 2g in single oral intake (PO), and 320mg single-take oral and azithromycin 2g in single-oral [63]. The cure rate was 100% for the combination gentamicin and azithromycin and 99.5% for Gemifloxacin and azithromycin. However, side effects, mainly gastrointestinal, have been frequently observed. Nevertheless, these two treatment regimens can be considered as an alternative in the event of failure of conventional treatment or in the presence of strains of resistance to cephalosporin [64]. In recent years, the activity of several an-

tibiotic derivatives on strains of *Neisseria gonorrhoeae* has been evaluated in vitro. Thus, the new Fluor ketolides azithromycin (macrolides) exhibits high activity against *Neisseria gonorrhoeae*, including ceftriaxone-resistant strains and multidrug-resistant strains. In addition, other molecules, such as solithromycin, Zoliflodacin, Gepotidacin and famulin, have also shown high activity on strains of *Neisseria gonorrhoeae* ceftriaxone. However, they are still in clinical trial [65,66].

Alternative therapies to combat *N. gonorrhoeae*, which is becoming increasingly resistant, are being developed. These alterna-

tives are mainly focused on preventing recurrent infections rather than on treatment such as intravaginal interleukin-12 (IL-12), studies evaluated a new potential strategy or probiotics using strains of vaginal *actobacillus* (*L. crispatus*, *L. gasseri* and *L. vaginalis*) whose metabolism can reduce the viability of Mr. Gonococcus. Monocaprine and myristoleic acid is a promising ophthalmic prophylaxis to the antibacterial treatment of neonatal conjunctivitis. Another alternative treatment that has gained prominence recently is bacteriophage therapy, as a therapeutic option alone or associated with currently used antimicrobials [66,67].

Guidelines	Infection anogénital*	Pharyngeal infection
Public Health Agency of Canada: Recommendations for Gonorrhoea Treatment 2016 [68]	Registered: Ceftriaxone 250 mg IM in single dose plus azithromycin 1 g per bone in single dose Cefixime 800 mg PO in dose plus azithromycin 1 g PO in single dose Alternatives: ••Spectinomycine** 2 g IM en dose unique plus azithromycin 1 g PO en dose unique Azithromycin 2g PO in single dose	Registered: ••Ceftriaxone 250 mg IM en dose unique as plus azithromycine 1 g per os en dose unique Alternatives: Cefixime 800 mg PO in single dose Plus azithromycine 1 g PO dose unique •• Azithromycine 2 g PO dose unique
European Guidelines 2012	Registered: Ceftriaxone 500 mg IM single dose plus azithromycin 2 g PO in single dose Alternatives: If ceftriaxone is not available or injection cannot be administered (Ex: patient refusal) - Cefixime 400 mg PO in single dose plus azithromycin 2g PO in single dose If azithromycin is not available or patient unable to swallow azithromycin: Ceftriaxone 500 mg intramuscular in single dose If there is a possibility or knowledge of resistance or allergy to broad-spectrum cephalosporins: Spectinomycin 2 g intramuscular in single dose plus azithromycin 2 g PO in single dose.	Registered: Ceftriaxone 500 mg IM single dose plus azithromycin 2 g PO in single dose Alternatives: If azithromycin is not available or patient unable to swallow azithromycin Ceftriaxone 500 mg IM en dose unique If antecedents allergy to cephalosporins or penicillin (sevère) and if <i>N. gonorrhoeae</i> is known quinolone-sensible== Ciprofloxacin 500 mg PO en dose unique ou ofloxacin 400 mg PO en dose unique If an allergy antecedent (severe) to cephalosporins or penicillin - Azithromycin 2 g PO in single dose

UK National Guidelines (BASHH) 2015 [69]	Registered: Ceftriaxone 500 mg IM in single dose plus azithromycin 1 g PO in single dose	Registered: Ceftriaxone 500 mg IM in single dose plus azithromycin 1 g PO in single dose
	Alternatives (if IM vs. indicated, or patient refusal): Cefixime 400 mg PO in single dose Spectinomycin 2 g IM in single dose ••Cefotaxime 500 mg IM en dose unique If sensitive to quinolones: Ciprofloxacin 500 mg PO en dose unique ou ofloxacin 400 mg PO en dose unique Azithromycin 2g PO in single dose	If sensitive to quinolones: Ciprofloxacin 500 mg PO in single dose or ofloxacin 400 mg PO in dose. Note: Spectinomycin has lower efficacy in cases of pharyngeal infections.

Table 3: Guidelines for Gonococcal Infection Treatments [65] (F). *site anogénital inclu: urethral, vaginal, rectal, et endocervical.

Conclusion

Infections with *Neisseria gonorrhoeae*, sexually transmitted infections, area public health problem both in its complications and in the growing emergence of multi-resistant strains. Moreover, the emergence of resistance to third-generation cephalosporins is particularly alarming in that they represent the last line of treatment, with no alternatives currently credible therapies. Therefore, the role of the biologist and clinician is necessary through sampling and diagnostic techniques management of gonococcus according to the various guides and algorithms evaluated. Similarly, a strategy to control sexually transmitted infections and to make sense of the concept of sexual health should be put in place for screening, effective treatment for patients and their partners.

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