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MANAGEMENT OF MULTI DRUG RESISTANT IN TREATMENT OF GONORRHEA : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *A significant worldwide public health issue, gonorrhea is made worse by antibiotic resistance.*

Aims : *This systematic review is to review the treatment of gonorrhea in patients with multi drug resistant of antimicroba.*

Methods: *This study demonstrated compliance with all requirements by means of a comparison with the standards established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.*

Result: *In the PubMed database, the results of our search brought up 4.511 articles, whereas the results of our search on SCIENCE DIRECT brought up 1.110 articles, our search on SAGEPUB brought up 1.738 articles. The results of the search conducted for the last year of 2014 yielded a total 1.464 articles for PubMed, 265 articles for SCIENCE DIRECT and 684 articles for SAGEPUB. In the end, we compiled a total of 5 papers, 3 of which came from PubMed, 1 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included five research that met the criteria.*

Conclusion: *In summary, globally, the prevalence of gonococcal infections is growing quickl. Most concerningly, N. gonorrhoeae is a significant contributor to the bacterial population that disseminates resistance to antibiotics.*

Keyword: *Multi drug resistant, gonorrhea*

INTRODUCTION

One of the most prevalent sexually transmitted diseases (STIs) is gonorrhea; in 2012, there were an estimated 78 million new cases. Gonorrhea cases have increased in countries with good surveillance; examples include the United Kingdom, where cases increased by 11% between 2014 and 2015, France, where cases among MSM (men who have sex with men) doubled between 2013 and 2015, the United States, where cases increased by 5% between 2013 and 2015, and almost all Australian states, where cases increased by 29%–146% between 2010 and 2014, all of which reflect longer-term trends. This rise is caused by a number of factors, including declining condom usage, rising urbanization and travel, low rates of infection diagnosis, and ineffective or unsuccessful treatment.[1–3]

High-, middle-, and low-income nations are all impacted by gonorrhea. Gonococcal infections are most common in Africa, where there are 50 and 100 new cases per 1,000 women and men, respectively, each year. With 395,000 cases in 2015—a 13% increase from 2014—it is the second most often reported notifiable infectious illness in the US. A comparable 15% increase was observed in Canada.[4]

In 40% of men, urogenital gonorrhea may be asymptomatic and presents mostly as urethritis. For almost half of the women, it also presents with no symptoms. Untreated urethral infections in males can result in urethral stricture, decreased fertility, and epididymitis. When symptoms do occur in women, they are vague and include dysuria, dyspareunia, abnormal vaginal discharge, and lower abdomen pain. When there are no obvious signs, infections go undiagnosed and untreated, which can have major consequences. In general, pelvic inflammatory disease (PID) affects 10%–20% of female patients, putting them at risk for infertility. Chorioamnionitis, premature membrane rupture, preterm delivery, ectopic pregnancies, and spontaneous abortions are pregnancy problems linked to gonorrhea.[5,6]

Both sexes commonly have extra-genital infections, which often happen without urogenital infections. While rectal and anal discomfort or discharge are common symptoms, rectal infections are typically asymptomatic. Although they seldom cause symptoms, pharyngeal infections can cause minor sore throats and pharyngitis. Because commensal Neisseria spp. transfer resistance characteristics to the pharynx, it is believed that resistance emergence occurs there more frequently than in other infection locations, despite the fact that bacterial numbers are typically lower. Additionally, gonococcal arthritis can accompany disseminated gonococcal infections. Despite their crucial role in the spread of illness, extra-genital infections are generally left untreated since they are often asymptomatic.[7]

Due to resistance, nearly all antibiotic classes used to treat gonorrhea are no longer effective. It is no longer possible to rely on sulfonamides, penicillins, early-generation cephalosporins, tetracyclines, macrolides, and fluoroquinolones. Resistance to extended-spectrum cephalosporins has been documented globally, endangering this last-remaining choice for first-line empirical monotherapy. With significant data gaps in Africa and Central Asia, the WHO Gonococcal Antimicrobial Surveillance Programme (GASP) discovered that resistance is mostly growing in Asia, North America, Europe, Latin America and the Caribbean, and Australia. The number of ESC treatment failure reports is increasing, and the first dual therapy treatment failure case was just published. There are currently reports of fluoroquinolone, high-level azithromycin, and cephalosporin resistance in a number of nations.[8,9]

With the possible exception of fluoroquinolone, the acquisition of several AMR features does not seem to impact biological fitness, leading to the maintenance of strains that are extensively drug-resistant (XDR) or multidrug-resistant (MDR) even in the absence of antimicrobial selection pressure. Regarding gonorrhea, multidrug resistance (MDR) indicates resistance to two or more of the following: macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides, and carbapenems, in addition to resistance to oral ESC and other current guideline therapies. XDR indicates resistance to spectinomycin and one or more ESC types, as well as resistance to tetracycline, aminoglycosides, carbapenems, macrolides, fluoroquinolones, penicillins, and tetracycline. In regions where resistance is more than 5%, the WHO advises modifying treatment protocols.[4]

Gonorrhea treatment is empiric (i.e., symptom-based, without identification of the causative organism or definition of its antimicrobial susceptibility profile) and syndromic, in accordance with WHO guidance. The majority of patients are managed in the community due to limited diagnostic access and capabilities in many settings. Treatment for the syndrome is based on the presence of clearly identifiable indicators (such as vaginal or urethral discharge) and the use of antibiotics that target most or all of the severe organisms causing the illness. Azithromycin and ESC combination treatment is now being used in numerous countries due to growing resistance to ESC monotherapy. However, there isn't much data to suggest that dual treatment truly slows the establishment of resistance, and strains resistant to azithromycin or ESC are already widely distributed.[10]

METHODS

Protocol

The author of this study ensured that it complied with the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to guarantee the accuracy of the results that are derived from the investigation. Thus, the specialists were able to guarantee that the research was as current as

feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

Criteria for Eligibility

In order to completse this literature evaluation, we looked at published research that discusses the treatment of gonorrhea in patients with multi drug resistant.This is done to enhance the patient's therapy management and to offer an explanation. This paper's primary goal is to demonstrate the applicability of the issues that have been noted overall.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) English must be used to write the paper. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) A few of the examined studies were released after 2013 but prior to the time frame considered relevant by this systematic review. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

Search Strategy

We used "multi drug resisntant" and "gonorrhea" out using the PubMed and SAGEPUB databases by inputting the words: "multi"[All Fields] AND ("drug resistance"[MeSH Terms] OR ("drug"[All Fields] AND "resistance"[All Fields]) OR "drug resistance"[All Fields] OR ("drug"[All Fields] AND "resistant"[All Fields]) OR "drug resistant"[All Fields]) AND ("gonorrheae"[All Fields] OR "gonorrheas"[All Fields] OR "gonorrhoea"[All Fields] OR "gonorrhea"[MeSH Terms] OR "gonorrhea"[All Fields] OR "gonorrhoeae"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

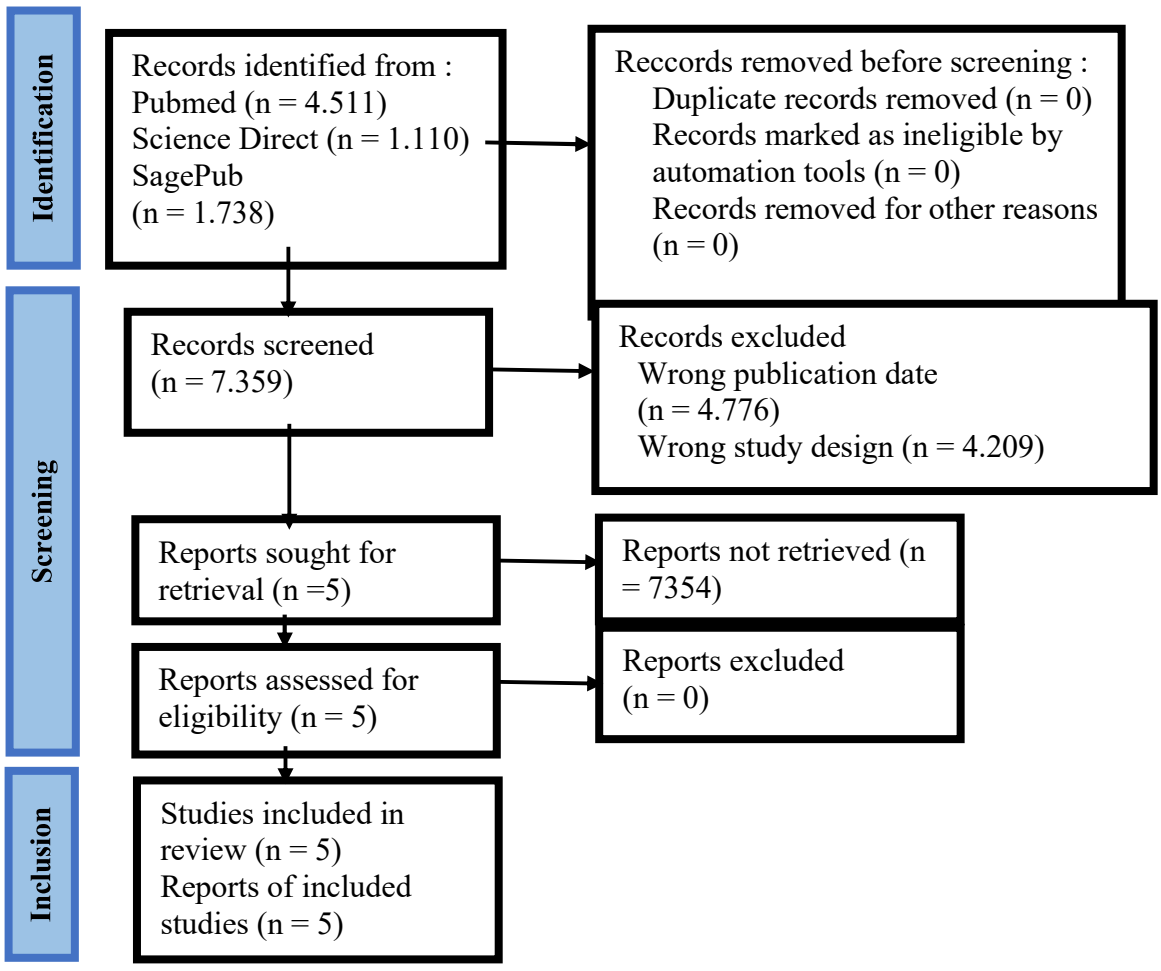

Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 4.511 articles, whereas the results of our search on SCIENCE DIRECT brought up 1.110 articles, our search on SAGEPUB brought up 1.738 articles. The results of the search conducted for the last year of 2014 yielded a total 1.464 articles for PubMed, 265 articles for SCIENCE DIRECT and 684 articles for SAGEPUB. In the end, we compiled a total of 5 papers, 3 of which came from PubMed, 1 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included five research that met the criteria.

Queiros, et al[11] (2020) showed that the current recommendations for treating N. gonorrhoeae remain very sensitive to antibiotics; nonetheless, as empirical treatments, ciprofloxacin, azithromycin (in monotherapy), and penicillin should be avoided.

Kirkcaldy, et al[12] (2014) showed that treatment for urogenital gonorrhea with gentamicin/azithromycin and gemifloxacin/azithromycin proved to be quite successful. Adverse gastrointestinal problems might prevent routine usage. When antibiotics made up of are not an option for a patient, these non-cephalosporin-based regimens could be a good substitute. There must be more gonorrhea therapy alternatives.

de Vries, et al[13] (2022) showed that when treating gonorrhea, a single dosage of 1000 mg ertapenem is not less effective than a single dose of 500 mg ceftriaxone. But gentamicin at a dose of 5 mg/kg (maximum 400 mg) is not less effective than ceftriaxone. Ertapenem warrants consideration for infections resistant to ceftriaxone and is a potentially efficacious substitute for treating anogenital N gonorrhoeae infections.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Queiros et al, 2020[11]	Portugal	Retrospective randomized study	440 patients	Our clinic detected 440 instances of N. gonorrhoeae infection between 2009 and 2018, showing a substantial annual increase ($p < 0.05$). The majority of cases (97.9%) involved men, and the median age was 25. Treatment with ceftriaxone with azithromycin was used in 88.7% of the patients. Over the course of the research, resistance to ciprofloxacin, tetracycline, and penicillin remained high.
Kirkcaldy et al, 2014[12]	USA	Randomized study	199 patients	In 202 evaluable people receiving gentamicin/azithromycin, 100% (lower 1-sided exact 95% confidence interval [CI] bound, 98.5%) and in 199

				evaluable participants getting gemifloxacin/azithromycin, 99.5% (lower 1-sided exact 95% CI bound, 97.6%) obtained microbiological cure. 10 out of 10 pharyngeal infections and 1 rectal infection were resolved by gentamicin/azithromycin; 15 out of 15 pharyngeal infections and 5 out of 5 rectal infections were resolved by gemifloxacin/azithromycin. Adverse gastrointestinal problems were prevalent in both groups.
de Vries et al, 2022[13]	Netherlands	Randomized non inferiority trial	2160 patients	93 (100%) of the 93 patients in the ceftriaxone group, 86 (99%) of the 87 patients in the ertapenem group, 79 (93%) of the 85 patients in the gentamicin group, and four (12%) of the 33 patients in the fosfomycin group cleared N gonorrhoeae in the primary per-protocol analysis (risk difference vs ceftriaxone: -0·01 [95% CI -0·08 to 0·05] for ertapenem and -0·07 [-0·16 to -0·01] for gentamicin). Ertapenem therefore turned out to be non-inferior to ceftriaxone. The ertapenem and gentamicin risk differences in mITT analysis compared to ceftriaxone were -0·08 (-0·17 to 0·003) and -0·11 (-0·21 to -0·04), respectively. In comparison to the ceftriaxone group, we found that a greater percentage of patients in the ertapenem group (58 [56%] of 103) and the fosfomycin group (36 [95%] of 38) experienced at least one adverse event.
Ross et al, 2019[14]	United Kingdom	Randomized non inferiority controlled trial	720 patients	It was not possible to show that gentamicin was non-inferior to ceftriaxone [adjusted risk difference for microbiological clearance: -6.4%, 95% confidence interval]. The two groups had comparable rates of genital infection clearance (94% in the gentamicin group and 98% in the ceftriaxone group), while the gentamicin group had lower rates of pharyngeal and rectal infection clearance. Gentamicin was associated with more reported injection

				site discomfort than ceftriaxone. The groups' side-effect profiles were similar to one another. There was just one major adverse event recorded, and it was determined that it had nothing to do with the trial drug. According to the economic research, gentamicin treatment is not cost-neutral when compared to standard care; on average, patients receiving gentamicin had greater treatment costs than those receiving ceftriaxone.
Petousis-Harris et al, 2017[15]	New Zealand	Retrospective case control study	14.730 patients	Out of the 24 clinics nationwide, 11 offered records. For analysis, there were 14 730 cases and controls, including 1241 gonorrhoea cases, 12 487 chlamydia cases, and 1002 co-infection cases. Significantly fewer people who received vaccinations than controls had higher case probabilities (511 [41%] vs 6424 [51%]; adjusted OR 0·69 [95% CI 0·61-0·79]; p<0·0001). After accounting for sex, geography, ethnicity, and deprivation, the estimated vaccination efficacy of MeNZB against gonorrhoea was 31% (95% CI 21-39).

Ross, et al[14] (2019) showed that the experiment was unable to show that gentamicin was not less effective than ceftriaxone in clearing gonorrhoea from all affected locations. Participants assigned to gentamicin had decreased clearance at pharyngeal and rectal sites than those assigned to ceftriaxone; however, clearance at genital sites was equivalent for both groups. More intense injection site discomfort was linked to gentamicin. Ceftriaxone and gentamicin, however, seemed to be well tolerated.

Petousis-Harris, et al[15] (2017) showed that it is the first time a vaccine has demonstrated any protection against gonorrhoea, and exposure to MeNZB was linked to lower rates of gonorrhoea diagnosis. These findings offer a proof of principle that can guide future research and development of meningococcal and gonorrhoea vaccines.

DISCUSSION

Gonorrhea is a disease that affects millions of individuals but is typically not fatal. Despite this, there is not enough funding or cooperation behind control efforts. There is presently rising fear that the possibility of incurable gonorrhea will materialize due to dwindling treatment choices in the broader context of antimicrobial resistance (AMR).

Globally, sexually transmitted diseases (STDs) continue to pose a serious threat to public health. The rise of antibiotic resistance in Neisseria gonorrhoeae, although being historically thought to be curable, is a severe issue at the moment. The study by Queiros, et al with 440 cases of gonorrhea that diagnosed in the center of medical, showed that resistance multiple drugs like penicillin, tetracycline and ciprofloxacine still increased through the period of the studies.[11]

The cornerstone of the currently advised gonorrhea therapy is ceftriaxone. Gonorrhea is a common sexually transmitted infection that is caused by Neisseria gonorrhoeae. First-line ceftriaxone-resistant strains are posing a challenge to the control of N gonorrhoeae. Alternative therapies are therefore required. For individuals with cephalosporin allergies or infections brought on by potentially cephalosporin-resistant Neisseria gonorrhoeae, backup therapy alternatives are desperately needed. Kirkcaldy, et al in their study of 15 to 60 years diagnosed with uncomplicated urogenital gonorrhea. This study showed that gentamicin/azithromycin with gemifloxacin.azithromycin effective as the therapy of urogenital

gonorrhea.[12] de Vries in their study also performed intramuscular 500 mg ceftriaxone (control group), intramuscular 1000 mg ertapenem, intramuscular 5 mg/kg gentamicin (maximum 400 mg), or oral 6 g fosfomycin were given to subjects at random (1:1:1:1). When treating gonorrhea, a single dosage of 1000 mg ertapenem is not less effective than a single dose of 500 mg ceftriaxone. But gentamicin at a dose of 5 mg/kg (maximum 400 mg) is not less effective than ceftriaxone. Ertapenem warrants consideration for infections resistant to ceftriaxone and is a potentially efficacious substitute for treating anogenital N gonorrhoeae infections.[13]

Ross, et al performed study with 720 participants with 81% were men. Adults between the ages of 16 and 70 who have been diagnosed with simple, untreated gonorrhea in the genitalia, throat, or rectal area based on a positive nucleic acid amplification test (NAAT) or a positive Gram-stained smear under microscopy.Although it was equivalent in both treatment groups, the loss to follow-up was 17%. At the baseline visit, 12% of patients had a negative NAAT for gonorrhoea; however, this was balanced throughout treatment groups and is unlikely to have influenced the trial's outcome. More intense injection site discomfort was linked to gentamicin. Ceftriaxone and gentamicin, however, seemed to be well tolerated.[14]

CONCLUSION

In summary, globally, the prevalence of gonococcal infections is growing quickl. Most concerningly, N. gonorrhoeae is a significant contributor to the bacterial population that disseminates resistance to antibiotics. There still need more research and studies about the treatment of gonorrhea in patients with multidrug resistant of antimicroba.

REFERENCE

[1] Fifer H, Natarajan U, Jones L, Alexander S, Hugher G, Golparian D, et al. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. N Engl J Med. 2016;374(25):2504–6.

[2] Paz-Bailey G, Mendoza MCB, Finlayson T, Wejnert C, Le B, Rose C, et al. Trends in condom use among MSM in the United States: The role of antiretroviral therapy and seroadaptive strategies. AIDS. 2016 Jul 31;30(12):1985–90.

[3] Newman L, Rowley J, Hoorn S Vander, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. Vol. 10, PLoS ONE. Public Library of Science; 2015.

[4] Alirol E, Wi TE, Bala M, Bazzo ML, Chen XS, Deal C, et al. Multidrug-resistant gonorrhea: A research and development roadmap to discover new medicines. Vol. 14, PLoS Medicine. Public Library of Science; 2017.

[5] Tsevat DG, Wiesenfeld HC, Parks C, Peipert JF. Sexually transmitted diseases and infertility. Vol. 216, American Journal of Obstetrics and Gynecology. Mosby Inc.; 2017. p. 1–9.

[6] Donders GGG, Desmyter J, De Wet DH, Van Assche FA. The association of gonorrhoea and syphilis with premature birth and low birthweight. Genitourin Med. 1993;69(2):98–101.

[7] van Liere GAFS, Hoebe CJPA, Duker-Muijrers NHTM. Evaluation of the anatomical site distribution of chlamydia and gonorrhoea in men who have sex with men and in high-risk women by routine testing: cross-sectional study revealing missed opportunities for treatment strategies. Sex Transm Infect. 2014;90(1):58–60.

[8] Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st Century: Past, evolution, and future. Clin Microbiol Rev. 2014;27(3):587–613.

[9] Grad YH, Harris SR, Kirkcaldy RD, Green AG, Marks DS, Bentley SD, et al. Genomic epidemiology of gonococcal resistance to extended-spectrum cephalosporins, macrolides, and fluoroquinolones in the United States, 2000-2013. Journal of Infectious Diseases. 2016 Nov 15;214(10):1579–87.

[10] Rice LB. Will use of combination cephalosporin/azithromycin therapy forestall resistance to cephalosporins in Neisseria gonorrhoeae? Sex Transm Infect. 2015;91(4):238–40.

[11] Queirós C, Borges Da Costa J, Lito L, Filipe P, Melo Cristino J. Gonorrhea in a Tertiary Care Portuguese Hospital: A 10-year Retrospective Study of the Evolution of Cases and Drug Resistance of the Isolates. Vol. 111, Actas Dermosifiliogr. 2020.

[12] Kirkcaldy RD, Weinstock HS, Moore PC, Philip SS, Wiesenfeld HC, Papp JR, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. Clin Infect Dis. 2014;59(8):1083–91.

[13] de Vries HJ, de Laat M, Jongen VW, Heijman T, Wind CM, Boyd A, et al. Efficacy of ertapenem, gentamicin, fosfomycin, and ceftriaxone for the treatment of anogenital gonorrhoea (NABOGO): a randomised, non-inferiority trial. Lancet Infect Dis. 2022;22(5):706–17.

[14] Ross JD, Harding J, Duley L, Montgomery AA, Hepburn T, Tan W. Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: the G-TOG non-inferiority RCT. Health Technol Assess. 2019;23(20):1–104.

[15] Petousis-Harris H, Paynter J, Morgan J, Saxton P, McArdle B, Goodyear-Smith F, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet. 2017;390(10102):1603–10.