Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

Revista Española de Quimioterapia
doi:10.37201/req/030.2024

Alfredo Maldonado-Barrueco[1,*]
Claudia Sanz-González[1,*]
David Grandioso-Vas[1]
Iker Falces-Romero[1,2]
Julio García-Rodríguez[1]
Inmaculada Quiles-Melero[1]

Allplex™ NG&DR (Seegene) utility for switching oral regimens with fluoroquinolones in gonococcal arthritis

[1]Clinical Microbiology and Parasitology Department. Hospital Universitario La Paz. Madrid, Spain.
[2]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain.

Article history
Received: 14 March 2024; Revision Requested: 10 May 2024; Revision Received: 14 May 2024; Accepted: 21 May 2024; Published: 1 July 2024

Sir,

Sexually transmitted infections (STI) by *Neisseria gonorrhoeae* (NG) have increased in recent years worldwide [1]. Gonococcal arthritis is a clinical manifestation of disseminated gonococcal infection (DGI). However, the DGI occurs only in 0.5-3% of patients [2]. Previously, we reported an increase of gonococcal arthritis in our health area from Madrid (Spain) [3].

The *gold standard* for the diagnosis of gonococcal arthritis is established by the growth of NG in the culture of synovial fluid, but its sensitivity can be diminished by the use of previous broad-spectrum antibiotherapy or delay in the microbiological processing due to the fact that NG is a fastidious microorganism difficult to culture. Moreover, NG is isolated in blood or synovial fluid in only 50% of patients with gonococcal arthritis, whereas mucosal swabs culture is positive in 80% of cases [4]. Until now, NG culture is importance not only for definitive diagnosis, but also for determining drug sensitivity [5]. The first-line treatment for NG infections is third-generation cephalosporins, such as intramuscular ceftriaxone or oral cefixime. Macrolides (azithromycin) are second-line treatments that should not be used in monotherapy. Treatment with fluoroquinolones (ciprofloxacin) may be an option in patients allergic or intolerant to third-generation cephalosporins, provided that *gyrA* mutations are not detected following the sexually transmitted infection guidelines [6, 7].

Guidelines for the diagnosis and treatment of septic arthritis in adults and children recommend ceftriaxone (first choice) 1g/24h or cefotaxime (alternative) 1g/8h IV. However, after clinical improvement, the switch to an oral agent guided by antimicrobial susceptibility is recommended for this clinical entity. Ciprofloxacin (500 mg/12h) is the first-line oral treatment, and cefixime (40mg/12h) is the second-line option to continue on an outpatient program [8]. Antimicrobial sensitivity screening for NG can be performed using phenotypic or genotypic methods.

Previously, our working STI group reported the prevalence of mutations associated with macrolide and fluoroquinolone resistance in NG from direct sampling in our population using one of commercially available CE kits (Allplex™ NG&DR Assay, Seegene®) [9]. The assay includes the A2059G mutation (23S rRNA) associated with high-level macrolide resistance and the C1126T mutation (23S rRNA) associated with moderate-level macrolide resistance. Resistance associated with fluoroquinolones is detected by the S91F (*gyrA*) mutation including in the assay. We reported a prevalence of 0.9% mutations associated with macrolide resistance, and 60% of mutations associated with fluoroquinolone resistance at the Hospital Universitario La Paz (HULP) from first-void urine, rectal, tectal, and oropharyngeal swabs [9]. Moreover, we compared the strip gradient diffusion test (phenotypic test) using EUCAST 2024 14.0 breakpoints with a molecular method using the NG&DR assay (genotypic test) from NG isolates [10]. Therefore, we reported that Allplex™ Assay could replace the gradient diffusion test for detecting fluoroquinolone resistance before treatment with ciprofloxacin in NG infections [10].

We report a migrant patient of a 68-years-old male from China. He showed fever (38.4°C), pain, and inflammation in both ankles with predominance in the left lower limb. After being discharged with anti-inflammatory drugs, the patient returned to the emergency department five days later with signs of synovitis in the left ankle, which required admission to the internal medicine ward. Blood tests showed leukocytosis (13,290; reference range 4,800–15,000 cells/mm^3) with 82% neutrophils and elevated C-reactive protein (251.6; reference range <1–0.5 mg/dL). Synovial fluid analysis of the left ankle analysis showed turbidity, hemorrhagic color, decreased glucose (62 mg/dL), and increased proteins (5.1 g/dL) in the absence of crystals and presence of neutrophils (95%). The pa-

Correspondence:
Alfredo Maldonado-Barrueco
Clinical Microbiology and Parasitology Department. Hospital Universitario La Paz. Madrid, Spain.
E-mail: alfredo.maldonado@madrid.salud.org
* Both authors have contributed equally to this work.

tient had maintained previous unprotected sexual intercourse one month ago.

The culture of synovial fluid on blood, chocolate, and chocolate agar PolyVitex mediums (BioMérieux®, Marcy l´Etoile, France) for 48 hours with 5% CO_2 in aerobic conditions atmosphere was negative. However, the Allplex™ 7 STI Assay (Seegene®) in combination with automated DNA extraction and PCR setup including NG, among other STI pathogens, was positive in the synovial fluid. Serologies for HIV, HBV, HCV, and syphilis (Atellica™, Siemens Healthcare Diagnostics®, Germany) were negative. In addition, following the recommendations of the STI guidelines for gonococcal arthritis, the STI screening including first-void urine, rectal and oropharyngeal swabs were performed using 7 STI Allplex™ with negative results [6]. The patient was treated with ceftriaxone 2g IV single dose and 1g IV/24h during 15 days. Due to non-growth of the NG isolate from the synovial fluid, Allplex™ NG&DR Assay was performed from a direct sample. The S91F (*gyrA*) mutation associated with fluoroquinolone resistance was not detected. Because of the absence of *gyrA* mutation detection included in the Allplex™ Assay and the good correlation between gradient diffusion and molecular methods in our NG isolates previously reported, the patient was discharged, and switched to an oral ciprofloxacin for 15 days. Subsequently, the patient was followed up in an outpatient clinic with success of the therapeutic treatment.

In conclusion, we report the utility of Allplex™ NG&DR (Seegene®) Assay for the detection of mutations associated with fluoroquinolone resistance (*gyrA*) directly from synovial fluid in a patient with non-growth of the NG strain in an environment with a high prevalence of ciprofloxacin resistance (~60-70%). This utility provides to an option for penicillin allergy patients, and reduces cefixime antibiotic consumption such as second-line treatment for switching oral treatment in gonococcal arthritis.

FUNDING

None to declare

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

REFERENCES

1. Salmerón P, Viñado B, Arando M, Alcoceba E, Romero B, Menéndez B, et al. Neisseria gonorrhoeae antimicrobial resistance in Spain: a prospective multicentre study. J Antimicrob Chemother. 2021;76(6):1523-1531. doi:10.1093/jac/dkab037
2. Britigan BE, Cohen MS, Sparling PF. Gonococcal infection: a model of molecular pathogenesis. The New England journal of medicine. 1985;312:1683–94. N Engl J Med. 1985;312(26):1683-1694. doi:10.1056/NEJM198506273122606
3. Maldonado-Barrueco A, Rico-Nieto A, Grandioso-Vas D, Ruiz M. Increase in gonococcal arthritis in Madrid, Spain, 2022-2023. Int J STD AIDS. 2024. doi: 10.1177/09564624241254877
4. Papp JR, Schachter J, Gaydos CA, Van B. Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014. 2014. MMWR Recomm Rep. 2014;63(RR-02):1-19.
5. Bardin T. Gonococcal arthritis. Best Practice & Research Clinical Rheumatology. 2003;17:201–8. Best Pract Res Clin Rheumatol. 2003;17(2):201-208. doi:10.1016/s1521-6942(02)00125-0
6. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually Transmitted Infections Treatment Guidelines, 2021; 70(4):1-187. Published 2021 Jul 23. doi:10.15585/mmwr.rr7004a1
7. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. Int J STD AIDS. 2020;31:4–15. doi:10.1177/0956462419886775
8. Benito N, Martínez-Pastor JC, Lora-Tamayo J, Ariza J, Baeza J, Belzunegui-Otano J, et al. Executive summary: Guidelines for the diagnosis and treatment of septic arthritis in adults and children, developed by the GEIO (SEIMC), SEIP and SECOT. Enferm Infecc Microbiol Clin (Engl Ed). 2024;42(4):208-214. doi:10.1016/j.eimce.2023.07.007
9. Maldonado-Barrueco A, Sanz-González C, Falces-Romero I, García-Clemente P, Cacho-Calvo J, Quiles-Melero I. Prevalence of mutations associated with macrolide and fluoroquinolone resistance in Neisseria gonorrhoeae with AllplexTM NG&DR Assay (Seegene®) in a tertiary hospital from Madrid, Spain. Rev Esp Quimioter. 2023;36(6):625-628. doi:10.37201/req/058.2023
10. Maldonado-Barrueco A, Sanz-González C, Falces-Romero I, García-Clemente P, Cacho-Calvo J, Quiles-Melero I. Comparison of gradient diffusion and molecular methods using AllplexTM NG&DR assay (Seegene®) for macrolide and fluoroquinolone screening resistance in Neisseria gonorrhoeae. Eur J Clin Microbiol Infect Dis. Published online February 26, 2024. doi:10.1007/s10096-024-04786-y