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Original Article

Azithromycin Treatment Failure and Macrolide Resistance in *Mycoplasma genitalium* Infections in Sofia, Bulgaria

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Abstract

Introduction: *Mycoplasma genitalium* is an established cause of sexually transmitted infections in men and women. Current guidelines recommend azithromycin and moxifloxacin as first- and second-line treatment, respectively. However, azithromycin treatment failure has been increasingly reported. The aim of this study was to determine the efficacy of azithromycin and alternative antibiotic regimens in a prospective cohort of *M. genitalium*-positive patients, and macrolide resistance mutations associated with azithromycin failure.

Materials and methods: Consecutive eligible *M. genitalium*-positive patients attending the National Center of Infectious and Parasitic Diseases in Sofia, Bulgaria between 1 January 2018 and 31 December 2020 were treated with azithromycin and retested by polymerase chain reaction 21-28 days after completion of the treatment. Cure was defined as *M. genitalium*-negative result on the test of cure. Cases failing azithromycin were treated with moxifloxacin and retested another 21-28 days after treatment. Pre- and post-treatment samples were assessed for macrolide resistance mutations by conventional DNA sequencing.

Results: Of 21 patients treated with azithromycin, 11 (52.4%) were cured. Pre- and post-treatment macrolide resistance mutations were detected in 10 (47.6%) patients, and all of them failed azithromycin. Moxifloxacin was effective in all cases failing azithromycin; and all were *M. genitalium*-negative at the test of cure after moxifloxacin treatment.

Conclusions: In this study a high azithromycin failure rate (47.6%) in an *M. genitalium*-positive cohort in association with high levels of pretreatment macrolide resistance was reported. Moxifloxacin was highly effective in treating macrolide-resistant infections. These findings necessitate implementation of new diagnostic and therapeutic strategies such as sequential antimicrobial therapy for *M. genitalium* guided by a macrolide-resistance assay.

Keywords

antimicrobial resistance, azithromycin failure, Bulgaria, *Mycoplasma genitalium*

INTRODUCTION

Mycoplasma genitalium was first isolated in 1980 in samples from patients with urogenital infections.[1] Because of the fastidious growth of the bacterium in culture, its etiological role as pathogen was in discussion for many years. Meanwhile, *M. genitalium* is an established agent of sexually transmitted infections such as nongonococcal urethritis (NGU) and cervicitis, and it is implicated in pelvic inflammatory disease[2,3] and increases transmission of human immunodeficiency virus[4]. Like other mycoplasma species, *M. genitalium* possesses a highly reduced genome and lacks a peptidoglycan-containing cell wall, so fewer classes of available antimicrobial agents are

effective including tetracyclines, macrolides and fluoroquinolones.

Although *in vitro* studies suggest that *M. genitalium* is highly susceptible against doxycycline, this drug has a poor clinical efficacy with microbiological cure rates between 22% and 45%.[5] Doxycycline is therefore not recommended for first-line treatment by European, US, and UK guidelines.[6-8]

Azithromycin given as an extended regimen is recommended as the primary choice for treatment of *M. genitalium* infections with a cure rate of approximately 85%.[6-9] However, the emergence of macrolide resistance is drastically decreasing the overall cure rate over the past decade with pooled cure rates in studies prior to 2009 of 85% compared to 67% in studies since 2009.[10] Macrolide resistance rates vary significantly geographically, but where azithromycin has been widely utilized, it is usually found in 30%–45% of samples.[11-15]

Moxifloxacin is the most commonly recommended agent as second-line antimicrobial treatment.[6-8] It is bactericidal and has a cure rate approaching 100% in infections with susceptible strains.[16] Unfortunately, resistance has developed with treatment failures in up to 12%, primarily in the Asia-Pacific region.[17]

AIM

This observational study has the aim to determine the *M. genitalium* microbial cure rate of azithromycin and to evaluate the contribution of macrolide resistance mutations to azithromycin failure. Effectiveness of moxifloxacin is determined in cases failing azithromycin.

MATERIALS AND METHODS

Recruitment and patient management

This observational study was conducted between 1 January 2018 and 31 December 2020 at the National Center of Infectious and Parasitic Diseases in Sofia, Bulgaria. Routine testing for *M. genitalium* was performed in patients with nongonoccocal urethritis (NGU), cervicitis and/or pelvic inflammatory disease, and sexual contacts of infected partners. Eligible participants were patients aged 18 years and older, diagnosed with *M. genitalium* and treated with azithromycin as first-line therapy. Participants were asked to abstain from sexual activity for the duration of study and to return for a test of cure (TOC) 21 days after completing treatment with azithromycin. Cases returning a TOC within 56 days of treatment completion were included in analyses to allow for delay in re-attendance for TOC. Along with the TOC, key data were collected to evaluate patient compliance and reinfection risk, including persistence of symptoms, adherence to antibiotic dosing regimen, adverse events and post-treatment sexual exposure to new or continuing partners. Where reinfection was suspected, index patients and contactable partners were recalled and retreated simultaneously with azithromycin. Only data following retreatment were included in analyses. Patients who remained *M. genitalium*-positive at the TOC following azithromycin, and who had no reinfection risk, were given moxifloxacin, and retested 21 days after completing treatment. All eligible participants were treated with antimicrobial therapeutic regimens recommended by the IUSTI 2016 European guideline on *Mycoplasma genitalium* infections.[7]

Azithromycin efficacy was measured as *M. genitalium* microbial cure following treatment with azithromycin. Microbial cure was calculated as follows: numerator = number of participants treated by azithromycin who were microbiologically cured of *M. genitalium* (defined as a TOC *M. genitalium*-negative at follow-up); denominator = all those treated with azithromycin for *M. genitalium* and tested at follow-up. For both the denominator and numerator, only those who were followed up were included.

Azithromycin failure was defined as *M. genitalium*-positive at TOC (with or without persistent symptoms) with no reinfection risk.

Laboratory methods

All examined specimens were sampled and stored as part of the routine STIs diagnostics (standard care) at National Center of Infectious and Parasitic Diseases as follows: forty millilitres of first-void urine specimen were centrifuged for 15 minutes at 2500 g and the pellet was resuspended in 200 μL of Tris-EDTA buffer solution (TE Buffer). Genital swabs were rotated 10 times in 400 μL of TE Buffer. Two hundred microliters of TE Buffer containing urine pellet or swab cells were then extracted using AmpliSens® MAG-NO-sorb-URO nucleic acid extraction kit (Ecoli s.r.o., Slovak Republic) as per manufacturer instructions. Detection of *M. genitalium* DNA was performed by AmpliSens® Mycoplasma genitalium-FRT.[18,19] All *M. genitalium* molecular diagnostics were performed on fresh samples during the study period 2018-2020. Immediately after *M. genitalium* diagnostics, the samples were stored at –79°C.

In January 2019, January 2020, and December 2020 currently available *M. genitalium*-positive samples were subjected to further molecular analysis. Firstly, positive samples were confirmed by PCR detecting the *MgPa* adhesion gene[20], then resistance-associated mutations in the 23S ribosomal RNA (rRNA) gene were identified using conventional Sanger DNA sequencing of the 147 bp amplicon produced with primers Mg23S-1992F and Mg23S-2138R, as described previously.[21] Sequence editing and multiple sequence alignments were performed using the software CLC Main Workbench, version 20.0.4 (https://digitalinsights.qiagen.com).

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Ethics and informed consent

Written informed consents were obtained from eligible patients for personal data collection and microbiological sample testing as required by national law and the Ethics Committee at the National Center for Infectious and Parasitic Diseases, Sofia, Bulgaria.

RESULTS

Twenty-five patients were diagnosed with *M. genitalium* during the study period **(Fig. 1)**. Three patients were ineligible as they did not receive azithromycin as first-line therapy. Of the 22 enrolled participants, 21 (95.5%) completed all aspects of the study. One participant did not provide follow-up samples within 56 days, although lab technicians made at least two attempts to contact those who failed to attend. None of the eligible participants was previously tested positive for *M. genitalium*.

Of the enrolled participants, 18 (85.7%) patients were men and 3 (14.3%) were women **(Table 1)**. Fifteen (83.3%)

Table 1. Characteristics of participants

	Male (n=18) n (%)	**Female (n=3) n (%)**
Median age (range)	32 (22-49)	28 (23-33)
Presentation		
Symptomatic	15 (83.3)	1 (33.3)
Asymptomatic contact	3 (16.7)	2 (66.7)
Specimen		
First-void urine	14 (77.8)	0 (0)
Genital swab	4 (22.2)	3 (100)

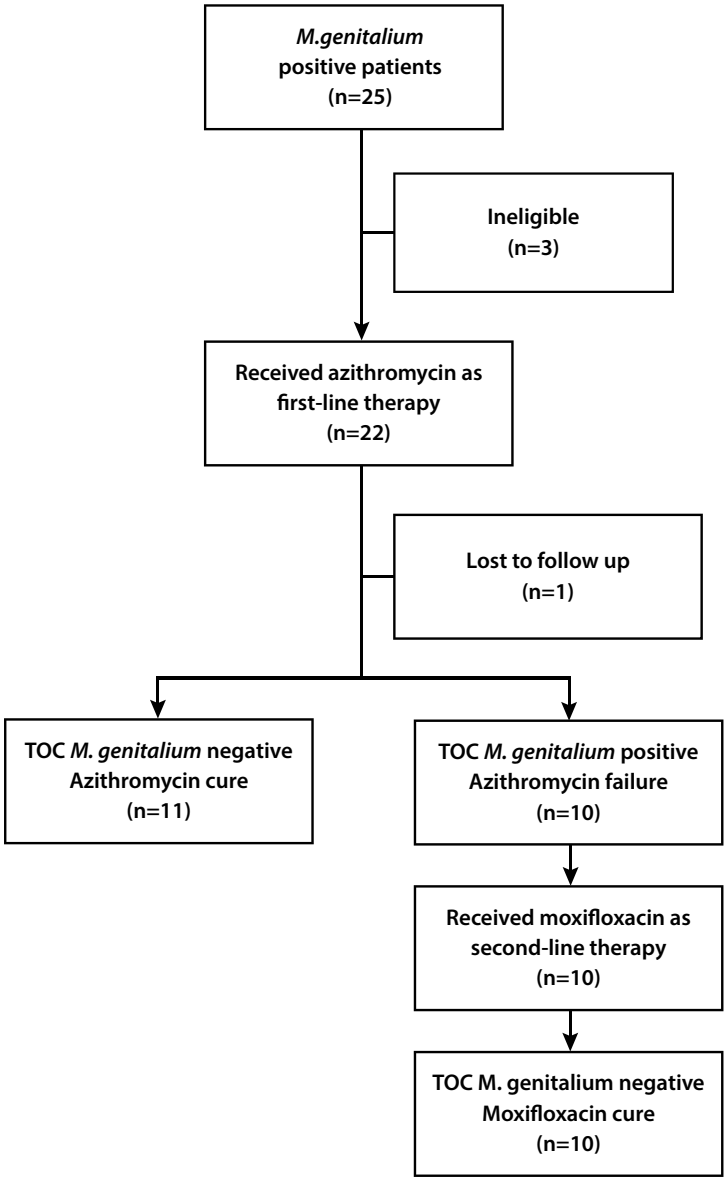

Figure 1. Recruitment and participation. TOC: test of cure.

M. genitalium-positive males had symptomatic NGU and 3 (5%) were asymptomatic contacts, whereas the 2 of *M. genitalium*-positive females presented as asymptomatic contacts of males and the remaining 1 symptomatic female reported vaginal symptoms.

Azithromycin treatment outcomes

Eleven cases had a *M. genitalium*-negative TOC, yielding an azithromycin cure rate of 52.4% (95% CI, 29.8% - 74.3%). Ten patients failed azithromycin (47.6% [95% CI, 25.7%-70.2%]) as they were *M. genitalium*-positive at TOC with no reinfection risk and received moxifloxacin as second-line therapy. Following treatment, one participant reported post-treatment sexual activity with an untreated partner. The index patient and the untreated partner were successfully recalled, retreated simultaneously with azithromycin, and recommenced participation, with only data following retreatment included in analyses.

Macrolide resistance mutations in pre- and post-treatment *M. genitalium*-positive samples

Overall, 23S rRNA gene sequences spanning positions 2071 and 2072 (2058 and 2059, *Escherichia coli* numbering) were obtained for the 21 pre-treatment *M. genitalium* samples in this study **(Fig. 2)**.

Additionally, 10 post-treatment samples from individuals with azithromycin treatment failure were tested for macrolide resistance mutations. On the pre-treatment samples, 11 (52.4%) cases had a wild type 23S rRNA gene sequence and had *M. genitalium*-negative TOC and azithromycin cure, respectively. All of the 10 participants with azithromycin treatment failure were shown to possess 23S rRNA gene mutations in pre- and post-treatment samples, consisting of A2072G (A2059G), A2071G (A2058G), and A2071T (A2058T). Amino acids substitutions in *E. coli*, to which those in *M. genitalium* respectively correspond, are given in the parentheses. In all of the resistant cases, mutational changes of the same type were detected in both the pre- and post-treatment samples indicating transmitted resistance **(Table 2)**. The most common mutation was A2072G (70%), followed by A2071G (20%) and A2071T (10%). No selected resistant *M. genitalium* strains were identified (wild type 23S rRNA gene sequence on the pre-treatment sample and macrolide resistant mutation detected on post-treatment samples).

Table 2. 23S rRNA gene sequence in pre- and post-treatment samples

23S rRNA	Pretreatment samples (n=21), No. (%)	Posttreatment sample (n=10), No. (%)
WT	11 (52.4)	0(0)
A2071G (A2058G*)	2 (9.5)	2 (20)
A2071T (A2058T*)	1 (4.8)	1 (10)
A2072G (A2059G*)	7 (33.3)	7 (70)

**E. coli* numbering

Effectiveness of alternative agents for *M. genitalium*-infections failing azithromycin

All 10 participants who failed azithromycin were given moxifloxacin and were *M. genitalium*-negative at TOC after the second-line therapy, yielding a moxifloxacin cure rate of 100%.

Figure 2. Comparison of partial sequences of 23S rRNA gene for *M. genitalium*-positive specimens detected in this study to the wild-type sequence (NCBI Reference Sequence: NR_077054.1) and macrolide resistant strains previously characterized at Statens Serum Institute (Copenhagen, Denmark) (Accession numbers M6321, M50367 and W68551).[22]

DISCUSSION

In this study, we report a high failure rate (47.6%) of azithromycin first-line therapy and high levels of macrolide resistance in *M. genitalium*-positive patients from Sofia, Bulgaria. Azithromycin failure was attributable to transmitted resistance and no selected resistance was detected after receiving azithromycin. Moxifloxacin was effective in all cases failing azithromycin.

Azithromycin remains the recommended first-line treatment for *M. genitalium* infection[6-8], although international data reveal that azithromycin is becoming less effective and macrolide resistance is increasing[23-28]. Data from Bulgarian studies remain very scarce, reporting *M. genitalium* solely prevalence with rates ranging from 0.29% to 2.45%.[29-31] To the knowledge of the authors, this is the first observational study for azithromycin failure and macrolide resistance in *M. genitalium*-positive patients from Bulgaria. The obtained in this study azithromycin cure rate of 52.4% is alarmingly low and raises concerns over the continued use of azithromycin in Bulgarian population, making the investigation of new diagnostic and therapeutic strategies a priority.

Failure of azithromycin is strongly associated with macrolide resistance mutations in the 23S rRNA molecule within the 50S subunit of the bacterial ribosome. These single-nucleotide polymorphisms in position 2071 and 2072 (2058 and 2059, *E. coli* numbering) in region V of the 23S rRNA gene confer high-level resistance to azithromycin.[22,32-34] According to recent scientific publications, differences in sexually transmitted infections management and treatment may distinctly influence antimicrobial resistance in *M. genitalium* among European regions.[35] For example, in countries like Sweden[36] where doxycycline is the preferred first-line treatment for NGU and *C. trachomatis*, the reported macrolide resistance is among the lowest in Europe (12.1%). On the contrary, high rates of macrolide resistance have been reported by countries using azithromycin as empirical treatment for NGU and *C. trachomatis*, including Spain (35%), France (58%), Netherlands (44.4%), Norway (41.4 %), Denmark (38%), and the United Kingdom (41%).[13,15,37-39] Presumably, the wide azithromycin use may account for the high prevalence of macrolide resistance in *M. genitalium* reported in this study. Additionally, Horner et al. registered recently moderate but convincing evidence that the extended azithromycin regimen for *M. genitalium* may be more effective than a single dose and is less likely to cause selection of macrolide resistance.[40] This could explain that no selected resistance was found in the present study as all of the eligible participants have received extended dosing of azithromycin.

Nevertheless, the detected high rate of transmitted macrolide resistance in this study hinders the effective treatment in a significant proportion of individuals. To address this issue, a combined diagnostic-resistance assay has been employed in clinical practice of most European countries.[41] The use of these combined tests allows implementation of so called resistance guided therapy, as *M. genitalium*-positive patients can then be prescribed azithromycin if macrolide susceptible or moxifloxacin if macrolide resistant. Resistance guided therapy is clinically demonstrated to improve patient cure rate and overall patient management, including reduction of time to cure and prevention of ongoing transmission.[42,43] This diagnostic strategy should maintain antimicrobial stewardship, until data on combination therapy and new classes of antimicrobials are available.

Fortunately, in the present study the efficacy of second-line treatment for *M. genitalium* infection was 100% and microbiological cure was achieved in all azithromycin failures. Moxifloxacin still has excellent efficacy in Europe[44] although resistance is increasing in Asia-Pacific region with sporadic cases of moxifloxacin failure occurring in Europe[45]. Using moxifloxacin as first-line therapy in all cases of *M. genitalium* is not recommended because future therapeutic options for multidrug-resistant strains are limited.[46] These options include only doxycycline with poor clinical efficacy and pristinamycin, which is not available in all European countries.

The impending loss of macrolides, and the emergence and inevitable spread of resistance to fluoroquinolones, first- and second-line recommended agents for *M. genitalium* in international guidelines[6-8], clearly necessitates new treatment approaches. While new classes of antimicrobials are urgently needed, antimicrobial combinations for *M. genitalium* to delay further emergence and spread of antimicrobial resistance, are also being investigated. Recent study demonstrates that >92% of *M. genitalium* infections can be cured in a population where two-thirds of cases are macrolide resistant and 20% of macrolide-resistant cases are fluoroquinolone resistant.[42] This was achieved with sequential therapy by pretreating with doxycycline and selecting a second antimicrobial with a macrolide-resistance assay. Replacing azithromycin with doxycycline for initial treatment of *M. genitalium* had the dual advantage of reducing overall use of azithromycin and reducing *M. genitalium* load.

The integration of combined molecular-based assays that detect *M. genitalium*, as well as resistance genes will greatly assist in the delivery of individualized therapy. This diagnostic approach, coupled with use of sequential therapy, is needed to halt the inevitable progression to a multidrug-resistant untreatable *M. genitalium*.

This study had several strengths including high recruitment and adherence rates and that all samples were successfully sequenced for macrolide resistance mutations. The main advantages were data availability from Bulgaria and resistance detected in both pre- and post-treatment samples indicating the strong selection induced by extensive antibiotic use. The main limitation was that there were more males in studied cohort and fewer females. This reflects the usually higher male attendance rates to laboratory service and limits evaluation of the contribution of the sex to azithromycin failure.

CONCLUSIONS

We report in the present study a high azithromycin failure rate (47.6%) in *M. genitalium*-infected patients from Bulgaria in association with high levels of pretreatment macrolide resistance. Despite emerging fluoroquinolone resistance in certain regions of the world, during the present investigation moxifloxacin was highly effective in treating azithromycin failures. These findings encourage the use of combined assays for simultaneous detection of *M. genitalium* and macrolide resistance mutations in order to optimize antimicrobial stewardship and control the selection and spread of resistances. Additionally, this study supports the need to perform antimicrobial resistance surveillance in *M. genitalium* at local level. In this situation, further investigations on new diagnostic and therapeutic strategies are required to fight against *M. genitalium* that may soon become untreatable with the appearance of multidrug-resistant strains.

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Неэффективность лечения азитромицином и резистентность к макролидам при инфекциях, вызванных *Mycoplasma genitalium*, в Софии, Болгария

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Резюме

Введение: *Mycoplasma genitalium* является установленной причиной инфекций, передающихся половым путем, у мужчин и женщин. Текущие руководства рекомендуют азитромицин и моксифлоксацин в качестве препаратов первой и второй линии соответственно. Однако всё чаще сообщается о неэффективности лечения азитромицином. Цель этого исследования состояла в том, чтобы определить эффективность азитромицина и альтернативных схем антибиотикотерапии в предполагаемой когорте *M. genitalium*-позитивных пациентов, а также мутации резистентности к макролидам, связанные с неэффективностью азитромицина.

Материалы и методы: Подходящие *M. genitalium*-положительные пациенты, последовательно посещавшие Национальный центр инфекционных и паразитарных болезней в Софии, Болгария, с 1 января 2018 г. по 31 декабря 2020 г., получали азитромицин и повторно тестировались с помощью полимеразной цепной реакции через 21–28 дней после завершения исследования. Излечение определяли как отрицательный результат теста на излечение, вызванный *M. genitalium*. Случаи неэффективности азитромицина лечили моксифлоксацином и повторно тестировали ещё через 21-28 дней после лечения. Образцы до и после лечения оценивали на наличие мутаций резистентности к макролидам с помощью обычного секвенирования ДНК.

Результаты: Из 21 пациента, получавших азитромицин, вылечились 11 (52.4%). Мутации резистентности к макролидам до и после лечения были обнаружены у 10 (47.6%) пациентов, и у всех из них азитромицин оказался неэффективным. Моксифлоксацин был эффективен во всех случаях, когда азитромицин был неэффективен; и все были *M. genitalium*-отрицательными в тесте на излечение после лечения моксифлоксацином.

Заключение: В этом исследовании сообщалось о высокой частоте неэффективности азитромицина (47.6%) в когорте *M. genitalium* в сочетании с высоким уровнем резистентности к макролидам до лечения. Моксифлоксацин оказался высокоэффективным при лечении резистентных к макролидам инфекций. Эти результаты требуют внедрения новых диагностических и терапевтических стратегий, таких как последовательная антимикробная терапия для *M. genitalium* под контролем анализа устойчивости к макролидам.

Ключевые слова

устойчивость к противомикробным препаратам, неэффективность азитромицина, Болгария, *Mycoplasma genitalium*