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1 **TITLE**

2 Initial failure of pristinamycin treatment in a case of multidrug-resistant *Mycoplasma*
3 *genitalium* urethritis eventually treated by sequential therapy.

4

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37

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43 **SHORT SUMMARY**

44 The initial failure of pristinamycin-based therapy was possibly linked to the presence of
45 A2062T mutation, and the *Mycoplasma genitalium* infection was finally cured after secondary
46 loss of this mutation.

47

48 **ABSTRACT**

49 We present a case of persistent *Mycoplasma genitalium* (MG) urethritis with documented
50 macrolide and fluoroquinolone resistance, and we describe the A2062T mutation in the 23S
51 rRNA gene, possibly associated with pristinamycin resistance. After several treatment failures
52 and loss of the A2062T mutation, MG urethritis was finally cured by a sequential antibiotic
53 treatment including minocycline.

54

55 **INTRODUCTION**

56 *Mycoplasma genitalium* (MG) is the most common cause of urethritis after *Neisseria*
57 *gonorrhoeae* (NG) or *Chlamydia trachomatis* (CT). European treatment guidelines recommend
58 azithromycin 1.5 g (500 mg followed by 250 mg daily for a total of 5 days) , and moxifloxacin
59 (400 mg daily for 7-10 days) as second-line treatment or in case of uncomplicated macrolide
60 resistant MG infection.¹ However in less than 10 years, more than 50% of strains have become
61 macrolide resistant and 5-10% fluoroquinolone resistant, in some parts of the world.^{2,3}
62 Hence sequential antibiotic treatment following susceptibility testing was suggested for MG
63 urethritis.^{4,5} Treatment began with doxycycline for 7 days meanwhile possible macrolide
64 resistance was detected. According to susceptibility testing, patients then received azithromycin
65 for 5 days or fluoroquinolones (sitafloxacin or moxifloxacin) for 7 days in case of macrolide
66 resistance. The rationale of sequential therapy beginning with doxycycline is to reduce the
67 bacterial load, to optimize the second antibiotic's effect while limiting the emergence of
68 resistance.

69 We report a case of multidrug-resistant MG urethritis successfully cured by several sequential
70 antibiotic treatments guided by susceptibility testing.

71

72 **CASE REPORT**

73 The patient was a 51-year-old Parisian man having sex with men, who had just started HIV pre-
74 exposure prophylaxis (PrEP). He consulted a general practitioner about urethral symptoms
75 (dysuria and discharge). After performing NG and CT nucleic acid amplification tests (NAATs)
76 on urine specimen, he received empirical therapy combining 7 days oral cefixime plus 1 g single
77 dose azithromycin (Table). NG and CT NAATs were negative. His symptoms persisted 12 days
78 later.

79 He was referred to a STI clinic, where the MG NAAT performed was positive. Moxifloxacin
80 was given but stopped after 48 hours because the patient reported tendon pain in lower limbs,
81 as a possible side effect of fluoroquinolones. He was given a sequential treatment with
82 doxycycline for 7 days followed by pristinamycin for 14 days, during which symptoms
83 decreased but relapsed afterwards.

84 Since his urethral discharge persisted, he was referred to our Infectious Diseases department,
85 at Pitié-Salpêtrière hospital in Paris. MG NAAT remained positive. Amplification and Sanger
86 sequencing of domain V of the 23S rRNA gene⁶ identified two mutations. The first one was
87 A2058T substitution (*Escherichia coli* numbering), known to be associated with macrolide
88 resistance. The second one was A2062T substitution, possibly associated with pristinamycin
89 resistance, as increased pristinamycin MICs were reported for *in vitro Mycoplasma pneumoniae*
90 strains harboring substitutions at A2062 position.⁷ Amplification and sequencing of the *parC*
91 gene didn't show any mutation associated with fluoroquinolone resistance.

92 The patient initially refused moxifloxacin despite his persistent symptoms, fearing a side effect.
93 He finally accepted a sequential treatment with doxycycline 200 mg daily for 7 days followed
94 by moxifloxacin 400 mg daily for 14 days without complication. A new screening of resistance
95 mutations performed during the moxifloxacin course found the previous A2058T mutation and
96 a new S83I mutation in ParC, associated with fluoroquinolone resistance. The A2062T
97 mutation was not detected anymore. He therefore received an additional sequential treatment
98 with minocycline for 21 days followed by pristinamycin for 14 days.

99 His urethral symptoms slowly disappeared. MG NAAT performed as test of cure 3 months after
100 completing the last sequential treatment was negative. The time period to obtain test of cure
101 was due to the patient's reluctance to come back to the hospital. MG NAAT performed 10 days
102 later remained negative, thus confirming microbial cure. Three-site NG and CT NAATs (urine,

103 rectal and pharyngeal sites) were all negative throughout this year, as well as HIV and syphilis
104 serologies. All sexual intercourse was protected by condom as reported by the patient.

105

106 **DISCUSSION**

107 As illustrated here, MG urethritis treatment can become very complex due to antibiotic
108 resistance. International guidelines now recommend doxycycline for 7 days instead of 1 g single
109 dose azithromycine as empirical therapy for urethritis and cervicitis, to preserve macrolide
110 susceptibility in case of undetected MG infection.⁸

111 For macrolide and fluoroquinolone-resistant MG strains, pristinamycin is the recommended
112 option in Europe,¹ with a success rate averaging 75%.⁹ But in case of failure, there is hardly
113 any alternative, with the possible exception of spectinomycin¹⁰ though unavailable in Europe
114 or minocycline, which cured 71% of cases.¹¹

115 Sequential treatment has also been suggested, consisting of doxycycline followed by an
116 appropriate antibiotic chosen according to the detected resistance mutations. Although
117 doxycycline cure failed in approximately 70% of cases, it could strongly decrease the bacterial
118 load hence substantially increase the second antibiotic's efficacy.⁵ Here we successfully
119 changed doxycycline for minocycline, which could be more effective on MG.¹¹

120 Combination therapy may also be an alternative for treating highly resistant MG. Doyle *et al.*
121 reported 75% of therapeutic success with doxycycline and pristinamycine combination therapy
122 in 73 macrolide-resistant MG cases.¹¹ Durukan *et al.* reported 11/12 cured MG infections using
123 doxycycline and sitafloxacin combination therapy, after pristinamycin failure.¹² However,
124 sitafloxacin is not available in France.

125 Importantly, the first part of sequential treatment gives time to perform a resistance genotypic
126 test, which requires a specialized molecular biology platform and takes several days. Since
127 resistance may vary depending on antibiotic pressure, we demonstrated here the relevance of

128 repeating the resistance screening. We described the A2062T mutation, possibly associated
129 with resistance to pristinamycin. Although mutations at 2062 position are not detected by any
130 commercial assays, the A2062T mutation has been reported a few times in MG, using 23S
131 rRNA amplification and sequencing.^{6,13} So far, this mutation has never been associated with
132 clinical resistance to pristinamycin in MG. However, we suggest it may be associated with
133 pristinamycin resistance, as the A2062G substitution is associated with increased pristinamycin
134 MICs for *M. pneumoniae*, the phylogenetically closest *Mycoplasma* species.⁷ Considering the
135 difficulties to grow MG, more studies focusing on pristinamycin treatment failure with
136 characterization of 23S rRNA mutations by Sanger sequencing are needed to confirm this
137 hypothesis.

138 **In conclusion**, we assume that the A2062T mutation is associated with pristinamycin resistance
139 in MG. We believe that the resistance profile of MG may vary over time, depending on the
140 different antibiotics received, and that antibiotic efficacy also depends on the bacterial load.
141 Repeated screening for genotypic resistance, combined with the use of antibiotics with the
142 highest antibacterial activity, could succeed in curing multidrug-resistant MG infections.

143

144 **TABLE. Therapeutic management and microbiological outcomes of the MG urethritis.**

Date	Day	Genito- urinary symptoms	Treatment	MG NAAT ^a	MG resistance mutations
08/23/2019	D0	Yes	Cefixime 200 mg 2/d 7 days AND azithromycin 1 g 1 day		
09/04/2019	D12	Yes		Positive	
09/07/2019	D15	Yes	Moxifloxacin 400 mg 1/d 2 days* THEN doxycycline 100 mg 2/d 7 days THEN pristinamycin 1 g 4/d 14 days		
10/11/2019	D49	Yes		Positive	A2058T ^b A2062T ^c
05/12/2020	D243	Yes	Doxycycline 100 mg 2/d 7 days THEN moxifloxacin 400 mg 1/d 14 days		
05/30/2020	D281	Yes		Positive	A2058T ^b S83I ^d
06/04/2020	D286	Yes	Minocycline 100 mg 2/d 21 days THEN pristinamycin 1 g 4/d 14 days		
09/10/2020	D384	No		Negative	
09/21/2020	D395	No		Negative	

145 NOTES. * Moxifloxacin was stopped due to tendon pain. a. NAAT, nucleic acid
146 amplification test. b. Mutation in 23S rRNA associated with resistance to macrolides,
147 *Escherichia coli* numbering. c. Mutation in 23S rRNA possibly associated with resistance to
148 pristinamycin, *Escherichia coli* numbering. d. Mutation in ParC associated with resistance to
149 fluoroquinolones, *Mycoplasma genitalium* numbering.

150 **DECLARATION OF CONFLICTING INTEREST**

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