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Which azithromycin regimen should be used for treating *Mycoplasma genitalium*? – A meta-analysis

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Key messages:

- There are no randomised controlled trials comparing the development of macrolide resistance in *Mycoplasma genitalium* infection between azithromycin 1g with azithromycin 1.5g over 5 days.
- Azithromycin 1g treatment is associated with 13.9% (7.7-20.1%) rate of failure and 12.0% (7.1-16.9%) risk of macrolide antimicrobial resistance.
- There is moderate but conflicting evidence that the 5 day regimen may be more effective and less likely to cause resistance.
- The difference in failure and resistance rates is 9.7% (95% CI: 4.3-15.0%, p=0.012) and 8.5% (95% CI: 3.2-13.8%, p=0.027) respectively.

Abstract

Background: There is increasing evidence that azithromycin 1g is driving the emergence of macrolide resistance in *M. genitalium* worldwide. We undertook a meta-analysis of *Mycoplasma genitalium* treatment studies using azithromycin 1g single dose, and azithromycin 500 mgs on day one then 250mgs daily for 4 days (5 day regimen) to determine rates of treatment failure and resistance in both regimens.

Methods: The online databases PubMed and Medline were searched using terms "*Mycoplasma genitalium"*, "*macrolide"* or "*azithromycin*" and "*resistance"* up to April 2016. Studies were eligible if they: used azithromycin 1g or 5 days, assessed patients for macrolide resistant genetic mutations prior to treatment, and patients who failed were again resistance genotyped. Random effects meta-analysis was used to estimate failure and resistance rates.

Results: Eight studies were identified totaling 435 patients of whom 82 (18.9%) had received the 5 day regimen. The random effects pooled rate of treatment failure and development of macrolide antimicrobial resistance mutations with azithromycin 1g was 13.9% (95% Confidence Interval: 7.7-20.1%) and 12.0% (7.1-16.9%) respectively. Of individuals treated with the 5 day regimen, with no prior doxycycline treatment, fewer 3.7% (95% CI: 0.8-10.3, p=0.012) failed treatment, all of whom developed resistance (p=0.027).

Conclusion: Azithromycin 1g is associated with high rates of treatment failure and development of macrolide resistance in *M. genitalium* infection with no pre-existing macrolide mutations. There is moderate but conflicting evidence that the 5 day regimen may be more effective and less likely to cause resistance.

Mycoplasma genitalium (MG) is an important, emerging sexually transmitted infection (STI) which causes 15-25% of acute non-gonococcal urethritis (NGU) in men and probably causes cervicitis, pelvic inflammatory disease, spontaneous abortion, preterm birth and tubal factor infertility in women.[1-3]

It is a relatively common ano-genital infection, with the majority of those infected being asymptomatic.[1, 3] About 1-3% of men and women in the general population are infected.[4-7] MG is detected more often in those infected with chlamydia, with 3-9% testing positive.[4-9]

Effective management strategies have been hampered not only by the lack of commercially available NAAT assays which have been evaluated to US Food and Drug Administration (FDA) approval standard combined with only limited validation for those assays which have been CE marked[1-2], but also by the poor treatment efficacy in eradicating MG with doxycycline 100mg twice a day for 7 days, or azithromycin 1g single dose which are the current first line treatments for NGU and cervicitis in the United Kingdom and the United States.[2, 10] Failure to eradicate MG with 7 days doxycycline 100mgs twice a day occurs in >50% of cases, and in 0-60% of cases treated with azithromycin 1g.[1, 11-13] Failure rates with azithromycin 1g have increased with time and a recent randomised controlled trial found no significant difference in treatment failure between azithromycin 1g and doxycycline 100mg twice a day for 7 days (40% vs 30%) .[13] This is probably due to the emergence of macrolide antimicrobial resistance in MG, worldwide.[1, 11-12, 14] A number of experts believe this may be a consequence of extensive use of azithromycin 1g for the treatment of STIs, as this regimen has been demonstrated to cause drug resistance in treatment failures.[1, 2, 11] An extended 5 day regimen of azithromycin 500mg on day one then 250mg daily for 4 days was introduced in the 1990s for the treatment of MG and has been demonstrated by two groups to have high efficacy (>95%) and until recently had not been associated with macrolide resistance.[15-17]

There was no information on risk of developing macrolide drug resistance with either azithromycin 1g or 1.5g extended regimen in wild type infections when compiling the 2015 United Kingdom NGU management guidelines.[18] Expert opinion was divided about discontinuing azithromycin 1g as first line treatment in favour of doxycycline 100mgs bd 7 days and/or changing to the azithromycin extended 5 day regimen for first line treatment. There are no randomised trials comparing azithromycin 1g to the 5 day regimen and the evidence supporting such a change was considered weak and no recommendation was made. A recent review by Manhart et al. noted that although the evidence was suggestive of slower emergence of resistance with the extended dose, the evidence was weak and further data was needed.[13] Undertaking a randomised controlled trial to demonstrate this would take 5-7 years to publish its findings and would be complicated by the high rates of MG macrolide antimicrobial resistance observed worldwide (13-100%).[3] We therefore undertook a review of the literature to determine treatment failure and macrolide resistance rates for patients without pre-treatment macrolide resistant genotype infections, using both the single dose azithromycin 1g regimen, and a 5 day 1.5g regimen. We also compared the treatment efficacies of both treatment regimens.

METHODS

Search Strategy

We undertook a review of the literature using the electronic online databases PubMed and Medline to identify published articles including the search terms "*Mycoplasma genitalium"* AND ("*macrolide"* OR "*azithromyicin*") AND "*resistance"* up to April 2016. Eligible studies were English Language prospective or retrospective treatment studies using azithromycin 1g or 500mg on day one then 250mg daily for 4 days, in which patients who failed treatment were assessed for MG macrolide resistant genetic mutations prior to, and after treatment. Both men and women were included. Women and men were combined for the purposes of the analyses. Macrolide antimicrobial resistance was defined as MG with a known macrolide resistance genotype involving a mutation at the nucleotide position 2058 (2071) and/or 2059 (2072) in the 23S rRNA gene.[12, 19] Patients were excluded from the primary analysis if there was no information on the pre-treatment specimen 23S

rRNA macrolide genotype or if they had been pre-treated with doxycycline. A secondary analysis was performed to include patients pre-treated with doxycycline as many patients will have received this as first line treatment for symptomatic NGU in Europe, prior to extended azithromycin.[2]

Data extraction and outcome

Identified studies were reviewed by KB, FG and PH and those meeting the inclusion criteria selected. Data was extracted by PH and FG and reviewed by SI for rates of failure and rates of macrolide resistance after treatment for MG with a course of azithromycin, in patients with macrolide-susceptible pre-treatment samples. These were defined as the percentage of individuals who returned for a test of cure who received a positive MG nucleic acid amplification test (NAAT), and of those who were still positive, the percentage who were found to have a macrolide resistance mutation in the 23S rRNA gene, respectively.

Analysis

We combined the data to determine the absolute rates of treatment failure and development of resistance of the two regimens. Rates of failure and resistance to the 1g regimen were quite variable across the different studies and therefore we next took a meta-analytic approach. With this approach we calculated the I^2 statistics to assess the percentage of variability in treatment failure and development of antimicrobial resistance estimates that could be attributed to underlying study heterogeneity rather than chance alone. If $I^2 > 25\%$ random effects meta-analysis was used to estimate the pooled rate of macrolide resistance development and if $I^2 < 25\%$ fixed effects meta-analysis.[11, 20] Both fixed effects and random effects meta-analysis were undertaken.

We compared the absolute rates of treatment failure and development of resistance between the two regimens. We then assessed the differences in these rates and calculated the associated 95% confidence intervals (95% CI) and p-values for the difference using Fisher's exact test. As there were only 2 studies which had both data on the 1g and 5 day regimens we performed a sensitivity analysis where we only considered the difference in rates between the 2 regimens in these 2 studies. This sensitivity analysis helps to avoid the problem of heterogeneity across the studies and provides a more

conservative estimate of the difference between the 2 regimens. We also undertook a separate sensitivity analysis including the additional patients treated with the 5 day regimen who had been pre-treated with doxycycline as it is possible prior treatment could have an effect on azithromycin efficacy. There were insufficient numbers to separately examine whether gender, age, symptoms or study type affected treatment outcome.

Data were analysed using Stata version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Study selection and characteristics

The review process is shown in figure 1. Seventy nine papers were identified and eight treatment studies met the inclusion criteria, (Table).[15, 17, 19, 21-26] Five were studies of patients tested for MG who were unselected or had NGU, cervicitis, and/or PID and/or were sexual contacts of infected partners and treated with azithromycin.[15, 19, 21-23] One was a study of a random sample of men with NGU treated with azithromycin 1g who were identified as MG-positive.[24, 25] One was a female only study designed to test incidence, organism load, and treatment failure after treatment with azithromycin 1g.[26] One was a prospective longitudinal cohort study comprising an observational study and a randomized treatment trial involving both men and women.[17] In only three studies was there information on the use of the extended azithromycin regimen 500mg then 250mg daily 4 days.[15, 17, 22]

Azithromycin efficacy

Four hundred and thirty-five individuals were identified of whom eighty-two (18.9%) had been treated with the extended 5 day regimen and 353 (81.1%) were treated with azithromycin 1g, (Table). Of individuals treated with azithromycin 1g, 47 (13.3%, 95% CI: 9.9-17.3%) remained MG-positive and of those 43 (91.5%, 95% CI: 80.0-97.6%) had a detectable mutation consistent with macrolide antimicrobial resistance. Of 82 individuals treated with the 5 day regimen, only 3 (3.7%: 95% CI: 0.8-10.3) failed and had a detectable mutation consistent with macrolide antimicrobial developed

resistance, which gave a difference in failure and resistance rate compared to 1g of 9.7% (95% CI: 4.3-15.0%, p=0.012) and 8.5% (95% CI: 3.2-13.8%, p=0.027).

Table Details of study type, follow-up and treatment outcomes

Table 1. Description of studies with details of treatment outcomes

Study	Study type, setting and year of data collection	Number of patients treated with the azithromycin 5 day regimen: number (%) who did not re-attend for test of cure	Number of patients treated with azithromycin 1 g and: number (%) who did not re-attend for test of cure	Number eligible for inclusion[#]	Time to test of cure	Specimen type	Treated with 5 day regimen			Treated with 1g regimen		
							Total	Failure	Resistance post-treatment	Total	Failure	Resistance post-treatment
Anagrius 2013[15]	Retrospective case note study of patients with MG. Swedish STD clinic. 1998-2005	72 male and 35 female: 9 (25.7%)	72 male and 22 female: 17 (12.7%)	139	Up to 52 weeks	Urethral swabs male and cervical swabs female	25	0 (0%)	0 (0%)	114*	7* (6.1%)	7* (6.1%)
Falk 2015[17]	Prospective longitudinal cohort study comprising an observational study and a randomized treatment trial. Swedish STD clinics. 2010-2014	25 male and 37 female: 9 (14.5%)	10 male and 5 female: 2 (13.3%)	56	Up to 26 days	Urine male and cervical swabs female	46	3 (6.5%)	3 (6.5%)	10	1 (10.0%)	1 (10.0%)
Gesink 2016[22]	Prospective, cross-sectional study of patients with MG. Toronto Sexual Health Clinic. 2013	12 male and 6 female: 3 (16.6%)		11	2-4 weeks	Urine male and female	11	0 (0%)	0 (0%)	0		
Bissessor 2015[23]	Prospective cohort study of		160 (male and female)[£]:	99	2-4 weeks	Urine male and genital tract	0			99	11 (11.1%)	11 (11.1%)

	patients with MG. Melbourne Sexual Health Centre. 2012-2013	5(3.1%)			swabs (high vaginal or cervical) female				
Couldwell 2013[19]	Retrospective case note study of patients with MG. Western Sydney Sexual Health Centre. 2008-2011	32 male and 1 female^ (34 episodes): 8 (23.5%)	12	Median 46 days (12-273 days)	urine or urethral swab	0	12	4 (33.3%)	3 (25%)
Ito 2011[25]	Retrospective case note study of men with MG-positive NGU. Urologic clinic in Sendai, Japan. 2006-2008	24 male:[&]	24	2-4 weeks	Urine	0	24	7(29.2%)	4 (16.7%)
Twin 2012[21]	Retrospective audit of MG-positive patients who returned for a test of cure. Melbourne Sexual Health Centre. 2007-2009	25 female and 86 males:[$]	66	Median 30 days (14-127 days)	urine or urethral swab men and cervical swab female	0	66	14 (21.2%)	14 (21.2%)
Walker 2013[26]	Prospective cohort study of patients with MG. Australian primary care clinics. 2007-	41 female: 9 (21.9%)	28	4 weeks	Vaginal swab	0	28	3 (10.7%)	3 (10.7%)

	2008							
Total		**435**	**82**	**3 (3.7%) (95% CI: 0.8-10.3)**	**3 (3.7%) (95% CI: 0.8-10.3)**	**353**	**47 (13.3%) (95% CI: 9.9-17.3)**	**43 (12.2%) (95% CI: 9.0-16.1)**

[#] Number of eligible study participants who had no pre-existing macrolide resistance mutations prior to treatment (see methods); * 3 additional patients who experienced treatment failure were excluded due to missing or inconclusive pre-treatment samples; [£]Of the 155 patients re-attending 112 (72.3%) were male; ^53 patients were diagnosed with MG infection. [&] Unclear how many men re-attended and tested negative; [$] The number of MG-positive patients treated with azithromycin 1 g who did not re-attend for a test of cure is not detailed.

The forest plot for treatment failure and antimicrobial resistance with azithromycin 1g is shown in figure 2a and b, respectively with details of the fixed effect and random effects meta-analyses. The I^2 value was 60.5% and 41.5% respectively which indicates moderate heterogeneity between effect estimates from different studies. The random effects pooled rate of treatment failure and development of macrolide antimicrobial resistance mutation(s) with azithromycin 1g was 13.9% (7.7-20.1%) and 12.0% (7.1-16.9%) respectively.

Of those with pre-treatment macrolide resistance mutations 1 of 1 failed the 5 day regimen[15] and 49 of 56,[23] 0 of 2,[26] 12 of 16,[21] 6 of 6,[19] 0 of 1[25] and 8 of 10[17] failed azithromycin 1g. Thus 76 of 92 (82.6% 95% CI 73.3% -89.7%) individuals with a macrolide resistance mutation failed treatment with azithromycin.

Sensitivity analyses

We calculated the differences restricted to the Anagrius et al. and Falk et al. studies and including the 3 men who had previously been excluded due to missing or inconclusive pre-treatment samples.[15, 17] This gave a difference in failure and resistance rate of 4.4% (95% CI: -0.02-11.2%, p=0.38) for 1g compared to the 5 day regimen.

We also undertook a separate analysis including the additional 56 patients treated with the 5 day regimen who had been pre-treated with doxycycline. Of 138 individuals treated with the 5 day regimen, no additional failures were observed. Thus 3 (2.2%: 95% CI: 0.5-6.2%) failed and developed resistance, an 11.1% (95% CI: 6.8-15.4%, p=0.0001) difference in failure rate and a 10.0% (95% CI: 5.8-14.2%, p=0.0002) difference in macrolide resistance rate compared to the 1g regimen.

DISCUSSION

This meta-analysis provides good evidence that an azithromycin 1g regimen is associated with rates of failure of 13.9% (7.7-20.1%), and of macrolide resistance of 12.0% (7.1-16.9%) in MG uro-genital infection in which no pre-existing macrolide resistance mutations are present. Although fewer

treatment failures were observed with the 5 day regimen in individuals with no prior doxycycline treatment, data from only three studies was available.[15,17,22] When combining the data in a crude way, this equates to a difference in failure rate of 9.7% (95% CI: 4.3-15.0%, p=0.012) and a difference in resistance rate of 8.5% (95% CI: 3.2-13.8%, p=0.027), which provides moderate evidence of a difference. Individuals with a pre-existing macrolide 23S rRNA gene mutation had a treatment failure rate of 82.6% (95% CI 73.6 -89%). These data are consistent with the hypothesis that the use of azithromycin 1g is driving the increase in prevalence of macrolide resistant MG genotypes.[11-12]

This is the first meta-analysis of the literature on azithromycin 1g treatment studies of MG to include only individuals in whom there was no evidence of a macrolide resistance genotype prior to treatment, and hence determine the rate of resistance in fully sensitive isolates. Eight studies of whom only 4 were prospective [17, 22, 23, 26] were identified and none involved a direct comparison of the two regimens. The latest a person could be included as a re-attendance ranged from 26-28 days for the four prospective studies [17, 22, 23,2 6] but varied considerably in the four retrospective studies with a range of 28-364 days.[15, 19, 21, 25]. In the four prospective studies the loss to follow-up ranged from 3-22% [17, 22, 23, 26] which was in general lower than the four retrospective studies with a range of 12% to 26% in two studies and unknown in the other two.[15, 19, 21, 25] As only those individuals who returned for a repeat test were included in this meta-analysis there are two potential biases. First, it is conceivable that a higher proportion of treatment failures were included in the outcomes, because it is likely, particularly in the retrospective studies, that patients successfully treated are less likely to return. Although Ito et al. observed that 3 out of 7 men who retested positive were asymptomatic.[25] Second, with a longer duration of follow-up it is possible that some patients who re-tested positive were actually re-infections. Only patients with no previous doxycycline treatment were included in the primary analysis as doxycycline could reduce the MG load and thus the potential for pre-existing micro-organisms containing macrolide resistance mutations.[12, 14, 27] Only three studies were identified with the 5 day regimen which precluded a rigorous meta-analysis of the efficacy of this regimen.[15, 17, 22] Finally some individuals who failed treatment and were

macrolide resistant did not have suitable pre-treatment specimens for resistance testing and were excluded from the analysis. As a sensitivity analysis we calculated the differences restricted to the Anagrius et al. and Falk et al. studies and including the 3 men who had previously been excluded due to missing or inconclusive pre-treatment samples.[15, 17] The study by Anagrius et al. was undertaken in specimens collected from 1998 to 2005. In 2006 no macrolide resistance mutations were detected in any MG-positive patients.[17] Including these individuals and comparing the treatment regimens in the only two studies which contained data on both the 1g and 5 day regimens also demonstrated a reduction in failure and resistance rates of 4.4% (95% CI: -0.02-11.2%, p=0.38).

Lau et al. recently undertook a systematic review and meta-analysis of azithromycin 1g treatment studies and demonstrated increasing failure rates which they attributed to emerging macrolide resistance over time.[11] Notably prior to 2009 the pooled treatment efficacy was 85.3% (82.3-88.3%), similar to 86.1% we observed in individuals with no prior macrolide resistance, and 67% (57.0-76.9%) after 2009. This is consistent with an increasing prevalence of macrolide antimicrobial resistance due to the widespread use of azithromycin 1g for treating urogenital tract chlamydia infection and its associated diseases, non-gonococcal urethritis (NGU) and cervicitis.[3, 11] A previous study by Bjornelius et al. demonstrated high efficacy (96%) of the extended 5 day azithromycin regimen and similar failure rate (14%) of azithromycin 1g to the pooled efficacy from our meta-analysis and that observed in all studies prior 2009.[11, 16] However, all patients receiving the 1g azithromycin regimen were Norwegian. Although no information on antimicrobial resistance is available, the study was undertaken in Norway and Sweden between 2002 and 2004. No macrolide resistance was identified in Sweden in 2006 but Norway had a 20-30% macrolide failure rate in 2005-6, which may explain the failure rate in the Norwegian patients.[15, 28] Two subsequent observational studies, which did not test for macrolide resistance prior to treatment, one from Norway undertaken 2005-2006[28] and one from Australia 2009-13[29] did not observe any difference in treatment efficacy between the azithromycin 1g and an extended 5 day regimen, 79% and 70%, 67% and 74% respectively. However, these findings could be explained by the presence of macrolide resistant micro-organisms in the population prior to treatment; the efficacy of both regimens is

effected in macrolide-resistant isolates.[1, 28] Recently Read et al in a retrospective observational study found that 4/34 (12% 95% CI 3–27%) patients with wild type infection had macrolide post treatment mutations with the azithromycin extended 5 day regimen.[30] The duration of follow-up was median 36 days (14-100 days) with a loss to follow-up of 63 (37%) of 169 men. Although they remark the macrolide mutation rate was similar to an historical control treated with azithromycin 1g and it is similar to the 12.0% from this meta-analysis there are a number of possible explanations for the apparent conflict with our findings. The confidence limits are wide and these are within the 95% CI for the macrolide post mutation rate observed in this analysis 3.7% (95% CI: 0.8-10.3) and may just be a chance observation related to the small size of the study. In addition, given the high loss to follow-up it is possible that the actual macrolide post treatment mutation rate was lower. Third, macrolide resistance was associated with men who have sex with men (MSM). This group was highly sexually active with a median of 3(2–6) sexual partners in the last 3 months prior to treatment. Seventy six percent of MG isolates were macrolide resistant in the local MSM population and although review of the notes suggested that re-infection was not the cause this remains a possibility as it was not a prospective study. Finally, an alternative but not mutually exclusive explanation is that in populations with high level of resistance mixed infections, not detected with the current methodologies, would tend to contribute to apparent resistance development. Taken together the conclusion of Read et al that the extended azithromycin 1.5g was no more effective than a single 1g dose should be viewed with caution and highlights the need for further high quality prospective studies using this regimen.[30] When the data from the Read study is added to this study and combined in a crude way no difference is observed between Azithromycin 1g and the extended regimen in post treatment macrolide mutations (p=0.09) but remains significantly different when patients with prior doxycycline are included (p=0.005).

Interestingly even in the presence of macrolide antimicrobial resistance our findings suggest 17% of individuals will test negative following treatment with azithromycin. This might be explained by other factors including either a temporary suppression of the infection and/or spontaneous fluctuations in the MG load which could lead to DNA shedding below the limit of detection, resulting in false

negatives.[17] In addition, four studies have observed spontaneous clearance of MG [31-34] suggesting that at least some of these individuals had resolved the infection. The most likely mechanism is the adaptive host immune response as it appears to be important in resolving infections, even following successful antimicrobial therapy.[35,36]

The findings provide moderate evidence that the extended 5 day azithromycin regimen (500mgs then 250mgs od for 4 days) is more effective than azithromycin 1g in treating MG. However we believe caution needs to be exercised in using the extended regimen as a replacement for azithromycin 1g and all patients followed up to establish that they have been cured as some patients will still fail treatment either due to pre-existent macrolide resistance or to its emergence following treatment and may be asymptomatic.[1-3, 25] Interestingly when the 56 patients with prior doxycycline treatment who were then treated with the extended regimen are considered, the superiority of the 5 day regimen is more pronounced with a 11.1% (95% CI: 6.8-15.4%, p=0.0001) difference in failure rate and a 10.0% (95% CI: 5.8-14.2%, p=0.0002) difference in macrolide resistance rate compared to the 1g regimen. This is probably as a result of a reduced micro-organism load following doxycycline treatment which will bias the comparison of this group with azithromycin 1g.[12, 13, 27] Nevertheless it provides strong support for the use of doxycycline 100mgs bd for 7 days as first line treatment in men with NGU, in whom MG is a common pathogen, with the extended azithromycin reserved for those who fail treatment.[2] There are no treatment studies on using other higher dose extended regimens such as azithromycin 1g then 250mgs od for 4 days and it is not possible to comment on whether other extended regimens are more efficacious than 500mgs then 250mgs od for 4 days.[2]

There are at least two hypothesis of why macrolide resistance emerges in MG following azithromycin 1g. The most likely mechanism is heterotypic resistance in which the use of azithromycin selects for pre-existing bacteria with macrolide resistance mutations which have arisen as a result of spontaneous genetic mutations.[12, 14] If this was the only mechanism both regimens would be expected to have similar rates of macrolide resistance following treatment, consistent with the recent finding of Read et al.[30] . Alternatively, it is possible that failure to eradicate micro-organisms, before sub- MIC levels

of azithromycin develop extracellularly with azithromycin 1g, may be occurring, enabling resistance to develop during treatment.[12, 14] Azithromycin 1g is cleared more rapidly from serum and extracellular fluid (where MG replicates) than 1.5g.[14, 37] Macrolides are not bactericidal and the duration of exposure to above MIC levels of azithromycin in vivo which is required to kill MG is unknown. Both hypotheses would be consistent with the observation that higher organism load prior to treatment has been associated with azithromycin 1g treatment failure and the findings from this analysis that the extended regimen is likely to be more efficacious.[26]

Conclusion

This meta-analysis has demonstrated that with wild type MG infection 13.9% will fail treatment with azithromycin 1g and 12.0% will develop macrolide resistance. These data are consistent with the hypothesis that the use of azithromycin 1g is driving the increase in prevalence of macrolide resistant MG genotypes which explains its reduced efficacy since 2009 and its use should be discontinued in MG-associated conditions.[1-3, 11] This study provides only moderate evidence that fewer patients will fail treatment and develop macrolide resistance with the extended 5 day regimen compared to azithromycin 1g which conflicts with the recent findings of Read et al.[30] An increasing pre-existent macrolide resistance, up to 100%, is seen in many countries.[1, 38] Initial doxycycline treatment will eradicate 20-40% MG strains, including macrolide resistant strains, reducing the need for Moxifloxacin treatment, in addition to possible reduced micro-organism load following doxycycline treatment. Further prospective studies comparing the extended azithromycin regimen with single dose, and azithromycin treatment following doxycycline are urgently needed.

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Contribution of Authors

PH conceived the study idea. PH, FG and KB undertook the literature searches and FG KB and PH reviewed the records for eligibility. PH and FG extracted the data which was checked by SI. SI undertook the statistical analyses. All authors contributed to the data interpretation. PH wrote the first draft with input from FG, HM and SI and revised subsequent drafts following critical review by all authors.

Conflict of Interests

None declared in relation to this submitted piece of work

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