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SHORT COMMUNICATION

# Five-day Azithromycin Treatment Regimen For *Mycoplasma genitalium* Infection Also Effectively Eradicates *Chlamydia trachomatis*

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*Chlamydia trachomatis* and *Mycoplasma genitalium* are the most frequent aetiologies of non-gonococcal urethritis (NGU) (1–3). There are no international management guidelines for *M. genitalium* infections. The recommended first-line treatments in NGU and *C. trachomatis* management guidelines are doxycycline, 100 mg twice daily for 7 days (oral), or azithromycin, 1 g stat (oral) (2, 3). Both these European guidelines are currently under revision. Doxycycline effectively eradicates chlamydial infection; however, it has a low eradication rate for *M. genitalium* infection (1, 4–6). With azithromycin 1 g, the eradication rate of *M. genitalium* has significantly decreased during recent years due to rapid emergence of resistance (1, 4, 6–8). Furthermore, treatment failures in >5% of patients treated for chlamydial infection with azithromycin 1 g have raised concerns (8–10). Homotypic azithromycin resistance in *C. trachomatis* has never been verified. Instead, it is hypothesized that an insufficient duration of azithromycin exposure and/or suboptimal azithromycin absorption in some patients may cause the clinical failures (11, 12). An extended azithromycin regimen, i.e. azithromycin 500 mg on the first day and 250 mg on the following 4 days, has been suggested as more or at least equally effective in eradicating *M. genitalium* and likely to mitigate the emergence of macrolide resistance in *M. genitalium* (1, 5–7, 13). In the European NGU and *C. trachomatis* management guidelines, this 5-day azithromycin regimen is recommended (2) or should be considered (3), respectively, when *M. genitalium* infection is verified or is suspected. Nevertheless, randomized controlled trials (RCTs) using the 5-day azithromycin regimen for treatment of *M. genitalium* infection have not been performed, and no data regarding the eradication rate of *C. trachomatis* have been published.

This study evaluated the eradication rate of *C. trachomatis* and *M. genitalium* with the 5-day azithromycin regimen in patients with dual uncomplicated urogenital infection.

## MATERIALS AND METHODS

At the Olafia STI Clinic, Oslo, Norway, among 3,790 patients positive for *M. genitalium* from 2010 to 2014, 390 (10.3%) had a dual infection with *C. trachomatis*. Most of these patients received doxycycline because of non-gonococcal urethritis or cervicitis, but 102 received azithromycin, 500 mg on day 1 and 250 mg on the following 4 days. All patients positive for *M. genitalium* are offered a test-of-cure (TOC) after 5 weeks. One patient treated after 36 weeks, and 16 patients who did not attend for TOC were excluded. Accordingly, 85 dually infected patients were included (Table I).

For nucleic acid amplification testing (NAAT) for *C. trachomatis* and *M. genitalium*, DNA was isolated from 200 µl of first void urine from males or vaginal ESwabs in Amies media using MagNA Pure 96 DNA and Viral NA Small Volume kit (elution in 100 µl buffer) on a MagNA Pure 96 System (Roche, Indianapolis, IN, USA). For detection of *C. trachomatis*, prior to January 2013, 25 µl of the DNA preparation were analysed with the COBAS TaqMan CT test v2.0 on a COBAS Taqman 48 (Roche Diagnostics). However, after December 2012, 10 µl of DNA was analysed using the GeneProof *C. trachomatis* PCR Kit (Geneproof, Brno, Czech Republic). DNA isolation and *C. trachomatis* NAATs were performed according to manufacturer's instructions. For *M. genitalium* detection, 10 µl of isolated DNA were tested with a real-time PCR (reaction volume 25 µl) with previously described primers and probes (14), on a 7900HT instrument (Applied Biosystems, Foster City, CA, USA).

## RESULTS

For the 54 females, the median age was 23.5 years (age range 18–47 years), and for the 31 males, median age was 26 years (age range 19–51 years), respectively. The delay from a positive test result to initiation of treatment varied from 4 days to 5 weeks, with a median time of one week in both females and males. The interval from initiation of treatment to TOC ranged from 4 to 43 weeks, with a median time of 6 weeks in both females and males.

Table I. *Summary of 85 patients dually infected with* C. trachomatis *(CT) and* M. genitalium *(MG), treated with the 5-day azithromycin regimen and returning for test-of-cure (TOC), 2010–2014*

| | Total, *n* | Males, *n* | Females, *n* |
|---|---|---|---|
| TOC performed | 85 | 31 | 54 |
| TOC negative for CT and MG | 61 | 23 | 38 |
| TOC positive for CT only | 3 | 1 | 2 |
| TOC positive for MG only | 18 | 6 | 12 |
| TOC positive for CT and MG | 3 | 1 | 2 |
| Among TOC positive cases: | | | |
| Possible or probable CT re-infection[a] | 5 | 2 | 3 |
| Possible or probable MG re-infection[a] | 6 | 2 | 4 |
| Probable CT failure[b] | 1 | 0 | 1 |
| Probable MG treatment failure[b] | 15 | 8 | 7 |

[a]Included 2 patients with probable re-infection for both CT and MG. [b]The patient with a probable CT treatment failure was also considered as a probable MG treatment failure.

The results of the TOCs and the interpretations of the positive TOCs are summarized in Table I. Thus, at TOC, 6 (7.1%) of the 85 patients were positive for *C. trachomatis* and 3 (50%) of these 6 patients were also positive for *M. genitalium*. Eighteen (21%) additional patients were positive for *M. genitalium* only. Of the 6 (7.1%) patients positive for *C. trachomatis*, 2 (2.4%) were considered to be probable re-infections, 3 (3.5%) as possible re-infections, and only 1 (1.2%) as a probable treatment failure. The latter was a female who had an infection with vomiting and fever during therapy. The 2 patients with probable *C. trachomatis* re-infections were again treated with the 5-day azithromycin treatment regimen and were negative for *C. trachomatis* at TOC (they remained positive for *M. genitalium*). One received azithromycin 1 g and was subsequently negative in TOC. The 2 remaining patients with possible *C. trachomatis* re-infections were treated with the recommended doxycycline regimen (3). The female with probable *C. trachomatis* treatment failure was negative for both *C. trachomatis* and *M. genitalium* at TOC after subsequent treatment with moxifloxacin, 400 mg daily for 7 days. Of the 21 (25%) patients positive for *M. genitalium* at TOC, 6 (7.1%) were considered as possible or probable re-infections and, accordingly, 15 (18%) of the initial 85 patients positive for *M. genitalium* were probable treatment failures (Table I).

Overall, taking into account only the patients in whom re-infection could be excluded, the eradication rate for *C. trachomatis* and *M. genitalium* was 98.8% (79/80) and 81% (64/79), respectively.

## DISCUSSION

This paper presents the first data revealing that the 5-day azithromycin treatment regimen used for *M. genitalium* in several countries also effectively eradicates *C. trachomatis* (eradication rate of uncomplicated urogenital infection: 98.8%). Only one probable treatment failure was identified and this patient had been vomiting and possibly not been able to absorb the azithromycin pills on the last days of treatment. The patient was treated successfully with 7-day moxifloxacin therapy. Worryingly, the eradication rate of *M. genitalium* was 81% (64/79), which probably reflects the high rates of pre-existing, endemic azithromycin resistance in the *M. genitalium* population circulating in Oslo, Norway. This treatment efficacy for *M. genitalium* was in line with a previous study reporting an eradication rate of 78% in Oslo (13). However, a much higher azithromycin failure rate has been reported from Australia (15). In general, it has been suggested that an extended course of bacteriostatic azithromycin is probably bactericidal to *C. trachomatis*, and in respiratory tract infections, azithromycin 1.5 g is administered over 3–5 days where it achieves therapeutic levels in target tissues for up to 10 days (11). Use of the 5-day azithromycin regimen when *M. genitalium* has been verified or is suspected might also mitigate the emergence of resistance in *M. genitalium* (1, 7, 11). A pragmatic extended azithromycin regimen could also be implemented, i.e. azithromycin, 1 g on the first day followed by 250 mg daily for 4 days, which includes the currently recommended azithromycin 1 g stat (immediate) dose (2–4, 8, 11).

Appropriate RCTs with extended azithromycin therapeutic regimens for both *M. genitalium* and *C. trachomatis* remain crucial. In such studies emergence of macrolide resistance in *M. genitalium* should be monitored, and TOC for both bacteria should be performed. Finally, new treatment options for *M. genitalium* infections are essential, and dual antimicrobial therapy, already introduced for gonorrhoea, might need to be considered.

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