

Single-Dose Azithromycin Treatment for *Mycoplasma genitalium*-Positive Urethritis: Best but Not Good Enough

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(See the article by Mena et al. on pages 1649–54)

The initial isolation of *Mycoplasma genitalium* from 2 of 13 men with urethritis in 1980 [1] led to a number of attempts to associate the bacterium with urogenital tract disease, but, because of the lack of specific and sensitive detection methods, many of the efforts were futile. It was not until the advent of polymerase chain reaction methods 10 years later [2] that clinical studies became feasible, and it took another 10 years to prove unequivocally that *M. genitalium* is a sexually transmitted cause of nongonococcal urethritis (NGU) in men. Moreover, because *M. genitalium* causes NGU independently of *Chlamydia trachomatis*, it partly filled a gap in our understanding of nonchlamydial NGU, explaining 20%–35% of these cases.

Although initial in vitro studies suggested that antibiotics of the tetracycline class were active, clinical experience soon demonstrated their inefficiency in producing both microbiologic and clinical cure. Several small observational studies as well as a recent larger study from Scandinavia [3] demonstrated that less than

half of *M. genitalium* infections were cured after doxycycline treatment, whereas azithromycin given as a single 1-g dose cured 80%–85% of the infections and azithromycin given at an extended dosage of 500 mg on day 1 followed by 250 mg daily on days 2–5 cured >95% of the infections. Two recently published observational studies of 120 Australian [4] and 183 Norwegian [5] *M. genitalium*-positive patients found that only 84% and 79%, respectively, were cured by a single 1-g dose of azithromycin.

However, the study by Mena et al. [6] in this issue of *Clinical Infectious Diseases* is the much-anticipated first randomized-treatment trial to investigate *M. genitalium* infection, and it confirms the findings of previous studies—even though a single 1-g dose of azithromycin was significantly more effective than multidose doxycycline, it eradicated only 87% of the *M. genitalium* infections. It is generally agreed that, for patients with gonorrhea, treatment should be expected to eradicate >95% of uncomplicated anogenital gonorrheal infections [7], and this has been extended to the treatment of *C. trachomatis* infection. Consequently, the currently recommended treatments for NGU are not optimal for the 15%–25% of NGU cases caused by *M. genitalium*. Evidently, this would lead to a considerable number of recurrent or persistent *M. genitalium*-positive NGU cases. Wikström and I [8]

found that, among men treated with doxycycline, >40% of those experiencing clinical failure were positive for *M. genitalium*, and all those treated with the 5-day course of azithromycin were cured. In contrast, when patients experience treatment failure with a 1-g single dose of azithromycin, the extended 5-day course of azithromycin appears to be much less efficient, as demonstrated by a cure rate as low as 34% among 23 patients in a recent study [5]. The finding that failure of azithromycin treatment as well as in vitro resistance to macrolide antibiotics is caused by single-base mutations in the *M. genitalium* 23S rRNA gene and that these mutations most often occur as a result of treatment with a single 1-g dose of azithromycin [9] is an obvious explanation for this observation. In patients experiencing failure of both doxycycline and the 5-day azithromycin regimen, moxifloxacin given at 400 mg daily for 7 or 10 days seems to be the only efficient treatment option [5]. If treatment of *M. genitalium*-positive NGU with single-dose azithromycin leads to treatment failure as well as the development of macrolide resistance, then the widespread use of this treatment modality would be brought into question. In the absence of standardized, readily available diagnostic tests for *M. genitalium*, there is a risk that moxifloxacin will be used uncritically for persistent NGU, which could result in the

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development of resistance to this antibiotic as well as adverse treatment events.

The study by Mena et al. is an important step in developing a rational therapy for *M. genitalium*-positive NGU. Future studies should learn from the present one that, despite clinical cure, *M. genitalium* may persist and result in recurrent NGU. Consequently, studies should have an extended follow-up period of at least 4–5 weeks. Furthermore, they should include patients with NGU of unknown etiology. As long as *M. genitalium* testing is available only to a limited number of sexually transmitted disease research clinics, optimal empirical NGU treatment should cover both *M. genitalium* and non-*M. genitalium*, nonchlamydial NGU. The group with the latter is commonly larger than both the chlamydial and *M. genitalium*-positive NGU populations and is an important but not very well investigated group of patients.

Future randomized studies should include as a third arm the 5-day azithromycin regimen, because this would be expected to eradicate *M. genitalium* from a larger proportion of patients, to potentially decrease the frequency of macrolide resistance, and to ultimately decrease the cost and disease burden associated with persistent or recurrent NGU. Unfortunately, the extended azithromycin regimen is not part of the large, ongoing MEGA (Mycoplasma Genitalium Antibiotic Susceptibility and Treatment) study [10], which is recruiting 1200 men

and randomizing them to the exact same treatment modalities as those of the study by Mena et al., nor is it included in a 4-armed randomized trial comparing the same 2 standard treatments with or without added tinidazole [11].

It is tempting to speculate that findings from studies of treatment efficacy in *M. genitalium*-infected men could be generalized to women. Although one study [3] suggested that doxycycline appeared to be more efficient in women, the difference did not reach statistical significance, and with increasing evidence indicating that *M. genitalium* causes pelvic inflammatory disease, trials investigating the treatment of this condition should also take *M. genitalium* into account.

In conclusion, the study by Mena et al. provides a clear-cut answer to the question of whether multidose doxycycline or single-dose azithromycin is most efficient for the treatment of *M. genitalium*-positive urethritis; undoubtedly, azithromycin is best. However, it is not good enough, and additional studies of new approaches are definitely needed.

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