Azithromycin for Rectal Chlamydia: Is it Time to Leave Azithromycin on the Shelf?...Not Yet

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Chlamydia trachomatis infection ("chlamydia") remains the most prevalent bacterial sexually transmitted infection worldwide. Although chlamydia most often occurs in the genital tract, it can also occur in the rectum. Rectal chlamydia is a relatively common infection in men who have sex with men (MSM), with reported prevalence rates of approximately 8%.1,2 Rectal chlamydia can lead to symptomatic proctitis and can increase the risk of HIV acquisition or transmission.

A fundamental component of chlamydia control efforts is the provision of highly effective therapy. The Centers for Disease Control and Prevention (CDC) currently recommends either azithromycin 1-g single dose or doxycycline 100 mg twice daily for 7 days for treatment of rectal chlamydia,3 but what is the evidence for this recommendation? The CDC recommendation stems not from robust studies showing equivalent efficacy of these treatment regimens for rectal chlamydia but, instead, from extrapolation of solid evidence supporting the efficacy of these regimens for urogenital chlamydia treatment and from clinical experience and expert consultation. A previous meta-analysis by Lau and Qureshi4 of 12 randomized clinical trials (RCTs) of azithromycin versus doxycycline for urogenital chlamydia treatment demonstrated these regimens to be highly efficacious, with microbial cure rates of 97% and 98%, respectively. However, most of these studies used culture for test of cure rather

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than the more sensitive nucleic acid amplification tests (NAATs) that are now CDC recommended for chlamydia testing.3

Unfortunately, to date, there have been no RCTs comparing the effectiveness of azithromycin versus doxycycline for rectal chlamydia, limiting our knowledge of the true efficacy of these treatment regimens for rectal chlamydia. However, there have been a limited number of clinical studies of these regimens for rectal chlamydia treatment whose findings collectively suggest that the doxycycline regimen may have a higher cure rate than the azithromycin regimen.5–9 Three were retrospective studies that evaluated just one of the treatment regimens and had significant limitations.5–7 For example, Steedman and McMillan6 reported an estimated azithromycin efficacy of 87% among 68 MSM, although the study was limited in that 8 of the 9 MSM with a repeat positive chlamydia test (polymerase chain reaction) after azithromycin treatment reported sexual activity between treatment and repeat chlamydia testing and also 3 of the 9 MSM with a repeat positive chlamydia test had their repeat test performed less than 21 days after therapy, introducing the possibility of a false-positive chlamydia test due to residual chlamydial DNA. Only one previous study has compared both azithromycin and doxycycline regimens for rectal chlamydia. Although not an RCT, Hathorn et al.9 compared both treatment regimens in a small prospective observational rectal chlamydia treatment study in men and women. They reported a difference in efficacy of these regimens for rectal chlamydia: 79% for azithromycin and 100% for doxycycline after adjusting for possible reinfection risk; however, the study also had significant limitations, including a high lost-to-follow-up rate (only approximately 50% of patients with rectal chlamydia returned to the clinic for a repeat chlamydia test).9

The limited prior evidence suggesting that the CDC-recommended doxycycline regimen may have a higher efficacy rate for rectal chlamydia than the recommended azithromycin regimen has now been further strengthened by findings from the study by Khosropour and colleagues10 reported in this issue. In a large retrospective study, Khosropour et al. evaluated rectal chlamydia treatment outcomes in a retrospective cohort of MSM diagnosed as having rectal chlamydia at a Seattle STD clinic between 1993

and 2012 who had received the CDC-recommended azithromycin or doxycycline regimens. The outcome of interest was persistent/recurrent chlamydia within 14 to 180 days after therapy. Of 1480 rectal chlamydia cases treated with azithromycin or doxycycline without a second drug active against C. trachomatis, 502 (34%) had a repeat chlamydia test within this time interval and were evaluable. The study found that persistent/recurrent rectal chlamydia rates were significantly higher among men treated with azithromycin compared with doxycycline, and the differences persisted across multivariate analyses as well as analyses of alternative follow-up intervals.

The study findings reported by Khosropour et al. provide some of the strongest evidence to date that a possible treatment disparity may exist between azithromycin and doxycycline for rectal chlamydia, yet the multiple potential limitations of their study, mostly inherent to the retrospective study design, should bring caution into interpretation of the study results and clinical decisions made based on the results.10 A major potential limitation of the study was that prescription of antibiotics was nonrandomized and the decision behind the prescribers' choice was unknown. It is possible that those deemed at highest risk for reinfection and/or nonadherence would be more likely to be prescribed single-dose therapy with azithromycin. Interestingly, Khosropour et al. reported a significant association between doxycycline use and both symptomatic infection and a proctitis diagnosis, in which one might postulate that providers more often chose the doxycycline regimen for what they considered a more clinically severe infection, reasoning that the longer duration of administered medication in the doxycycline regimen might be more effective. Another potential limitation was the high rate of treated patients who did not return for a repeat chlamydia test, which could have influenced the results. Another potential limitation was that chlamydia culture was more often used in men treated with doxycycline compared with the more sensitive NAAT (which detects more chlamydia than culture) being used more often in men receiving azithromycin (only 19 men treated with doxycycline had NAAT for repeat chlamydia testing); although this likely reflects the evolving diagnosis and treatment practices of the STD clinic practitioners, it may have also influenced the results. Repeat chlamydia testing with NAAT at less

than 21 days from urogenital chlamydia treatment initiation may occasionally yield false-positive results due to residual chlamydial nucleic acids that have not cleared from the genital tract, and there has been insufficient evaluation of the nucleic acid clearance rate after rectal chlamydia treatment to know the expected chlamydia clearance rate and whether it differs after doxycycline compared with azithromycin.8 Another potential limitation is that more than 20% of men studied were HIV infected, although the proportion of HIV-infected men did not differ by treatment regimen; we do not know if there was any difference in the proportion of men with AIDS in the different treatment regimen groups, and it is not known whether chlamydia treatment outcomes differ in persons with immunosuppression. Finally, worth mentioning is that the C. trachomatis outer membrane protein A (aka MOMP) serotype/genotype of the chlamydial strains was unknown in this study, which is important because lymphogranuloma venereum (LGV) may have occurred in this patient population, and not only is it unknown how effective either of the treatment regimens would have been for LGV, but also there is limited evidence suggesting a longer time to nucleic acid clearance after LGV treatment initiation compared with treatment of non-LGV chlamydia8; the CDC-recommended treatment regimen for LGV is a 3-week course of doxycycline.3

Should the study findings of Khosropour et al.10 lead to an immediate change in our treatment practices for rectal chlamydia? Is it time to leave azithromycin on the shelf and only use doxycycline for treatment of rectal chlamydia? We advise “No” at this time based on the fact that the most comprehensive rectal chlamydia treatment data to date have been derived from this retrospective study, and there has been no RCT for rectal chlamydia. An RCT would eliminate prescribing biases, should provide more equality in the potential confounders of rectal chlamydia treatment outcomes, and is a more appropriate study design for assessing “superiority” or “noninferiority” of treatment regimens. OmpA genotyping could be incorporated in the RCT (to identify LGV strains), and more information could be collected on the immune status of HIV-infected patients if included in the RCT. Another reason not to abandon azithromycin for rectal chlamydia treatment at this time is that the single-dose administration limits the potential treatment nonadherence that is sometimes seen with the multidose doxycycline regimen. A

previous study by Augenbraun et al.11 demonstrated that only 16% of STD clinic patients were fully compliant (based on a Medication Event Monitoring System cap methodology) with the 7-day doxycycline regimen for urogenital chlamydia treatment; although repeat chlamydia detection was uncommon (approximately 6%) after the doxycycline treatment, it was associated with 2 or more 24-hour intervals when doxycycline was not taken or when less than 11 of the prescribed 14 doxycycline doses were taken (based on Medication Event Monitoring System cap readings).

We do acknowledge the further increase in concern about azithromycin's efficacy for rectal chlamydia based on the study findings of Khosropour et al.,10 which should strike of a sense of urgency among sexually transmitted infection researchers for the need for an RCT to address this concern because of the morbidity associated with rectal chlamydia (proctitis, increase in HIV transmission risk, etc) and the potential impact on rectal chlamydia control efforts. If an RCT did demonstrate a significant difference in the treatment regimens, then additional studies would be needed to understand the factors that may be contributing to the efficacy difference, such as antimicrobial resistance and antimicrobial concentration at the rectal mucosa. However, until a rectal chlamydia RCT is performed, it seems reasonable to continue to recommend azithromycin as a treatment option for rectal chlamydia, especially for those in whom treatment adherence is a concern.

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