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Azithromycin efficacy in asymptomatic rectal chlamydial infection in MSM: A more definitive answer soon?

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Azithromycin efficacy in asymptomatic rectal chlamydial infection in MSM: A more definitive answer soon?

Asymptomatic rectal *Chlamydia trachomatis* (CT) infections are common among men who have sex with men (MSM) (1), and frequently exist apart from urethral infections: up to 88% of those with rectal CT are negative at the urethra (2). The Centers for Disease Control (CDC) recommends rectal screening for CT among MSM at least yearly, and for those positive, rescreening in ~3 months due to a substantial rate of repeat infections (3). Currently, CDC treatment recommendations for asymptomatic rectal infections include either azithromycin 1 g orally as a single dose, or doxycycline 100 mg orally bid for 7 days (3). Treatment recommendations for symptomatic proctitis and severe proctocolitis differ because pathogens other than *C. trachomatis*, including *Neisseria gonorrhoeae* and herpes simplex virus, can cause these syndromes. Severe disease also suggests lymphogranuloma venereum, caused by LGV strains of *C. trachomatis*, for which 21 days of doxycycline is recommended.

Notwithstanding the CDC guidelines, the best treatment for asymptomatic rectal infections in MSM is not clear. A number of observational studies, both retrospective and prospective, have been reported since 2009. A systematic review and metaanalysis of 8 of these studies estimated a pooled efficacy for azithromycin of 82.9%; 5 of the studies also included doxycycline, with an estimated pooled efficacy of 99.6% (4). The largest experience among these was a retrospective study in Seattle where among MSM with repeat CT testing within 90 days of treatment, the adjusted relative risk for persistence/recurrence among azithromycin treated men was 5.2 (95% CI, 1.3-21) (5). A follow-up report of one of the studies in the metaanalysis comprised 532 doxycycline-treated men and women with rectal CT, and reported an estimated failure rate of 0.9% (6). Finally, a recent retrospective experience among asymptomatic rectal CT in MSM reported an azithromycin efficacy of 83.6% among 171 azithromycin treated individuals. Of note, biomarkers including *ompA* sequencing and multilocus sequence typing (MLST) and behavioral data were employed to help discern treatment failure from reinfection (7). This study also suggests that organism load estimated at the index infection prior to treatment is associated with treatment failure.

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Another contribution to this literature is the report in this issue by Smith et al. (8). In a prospective observational cohort within the REACT randomized trial in Australia, repeat CT infections were sought among men who have sex with women (MSW) (n=89), women who have sex with men (WSM) (n=100) and MSM (n=101) who were CT-infected at baseline and treated with single-dose azithromycin. In MSW and WSM, urogenital sites were sampled, and among MSM, urogenital and rectal sites. The authors employed an algorithm which included detailed behaviors, *ompA* genotyping and MLST to distinguish treatment failures from likely reinfections. They found that treatment failures differed between the pooled MSW/WSM groups (2.6%) as compared to MSM (8.9%); among MSM most treatment failures were at the rectal site. Although the number of repeated infections evaluated was relatively small (n=43), the analyses are detailed and carefully done. Initial organism load in MSM again was associated with treatment failure. As previously reported, CT genotype distributions differed between the pooled MSW/WSM groups and the MSM group—another research question is whether this is a product of a largely non-intersecting epidemiology, or of bacterial factors that provide a competitive advantage at the rectal site. Finally, the study result supports the contention that azithromycin is less effective at the rectal site as opposed to genital sites.

The available literature, although observational in nature, points to the possibility of superior microbiological effectiveness of doxycycline over azithromycin in rectal CT infections in MSM. Recommendations for treatment of asymptomatic rectal CT have shifted to favor the doxycycline regimen in both Australian and European guidelines (9, 10). Is this then a settled issue? The observational studies above have limitations. Most studies lacked biomarkers and many lacked detailed behavioral information to distinguish reinfection from treatment failure; some were non-comparative wherein only one treatment regimen was reported; several were retrospective; many had high loss-to-follow up rates; some included and pooled both men and women; and many included both symptomatic and asymptomatic persons. In addition, in some cases diagnostic tests differed, important because culture is less sensitive than nucleic acid amplification tests (NAATs). Finally, with the exception of one study that compared azithromycin to doxycycline in a before-and –after comparison when clinic treatment policy was changed, treatments were not randomized or standardized, and the reasons that clinicians selected a regimen are not known.

Despite the fact that the currently available retrospective and prospective observational studies all seem to point to a lower response rate to azithromycin, best evidence in the form of a randomized controlled trial (RCT) does not yet exist. The good news is that such an RCT of azithromycin versus doxycycline for the treatment of asymptomatic rectal infection in MSM is underway in Australia. The study protocol has been recently published (11). The Rectal Treatment Study aims to recruit 700 MSM with rectal detection of CT by NAAT, without symptoms of proctitis. Treatment will be randomized and double-blind. The primary outcome is CT detection by NAAT at 4 weeks. Secondary outcomes include use of behavioral and molecular analyses as methods for estimating repeated detections that are likely treatment failure as opposed to reinfection. The trial began recruiting in August 2016 with the goal of completing recruitment in 3 years.

Should doxycycline prove more effective in an RCT setting, many providers would be concerned about adherence to the 7 day regimen, and fear that “use-effectiveness” in the real world may be less favorable and abrogate any advantage over single-dose therapy. Indeed, 2 studies using the Medication Event Monitoring System to assess adherence to 7-day doxycycline courses in the STD clinic setting suggested low rates (16-25%) of complete adherence (12, 13). However, the Bachmann study (13) reported a microbiological treatment success of 94% based on NAAT, despite poor adherence. More recently, in the context of an RCT comparing azithromycin and doxycycline in the treatment of NGU, a combination of written patient logs and computer-assisted self-interviews was used to assess adherence; a single missed dose was defined as non-adherence (14). Among men with chlamydial urethritis, 1/37 men with complete adherence failed doxycycline, as opposed to 2/10 with non-adherence; the 95% confidence interval of adjusted relative risk was very wide (1.00-89.2). Perhaps reassuring is that doxycycline efficacy in the observational studies ranges from 90.5 to 100%, with 5 of the 6 studies clustered in the 96-100% range (4, 6).

Why might azithromycin be less effective than doxycycline at the rectal site, and why might azithromycin be less effective in eradicating CT detected at the rectal site, as opposed to urogenital sites? Although differential antibiotic tissue penetration or other factors may be involved, it is worth reconsidering the mode of transmission of CT which results in rectal shedding. The operative assumption that drives rectal screening recommendations is that asymptomatic rectal infections in MSM (and WSM) result from direct inoculation by insertive anal intercourse. Many undoubtedly are, but the possibility of acquisition of CT via oral sexual activity (fellatio, anilingus) causing asymptomatic gastrointestinal (GI) tract infection resulting in rectal shedding must also be considered. Rank and Yeruva (15) reviewed the extensive available data for both experimental animal models and for natural chlamydial infections in veterinary animals; these demonstrate that an asymptomatic GI reservoir, commonly at the cecum, is present in every system studied. The immune response to GI involvement appears to wane rapidly despite presence of ongoing infection. Rank and Yeruva furthermore have shown that cecal infection in mice commonly fails treatment with azithromycin, while genital infection is eradicated; the reason for this disparity is not clear. Doxycycline treatment effectively clears both sites. The parallels with available clinical observations are striking. It is reasonable to hypothesize that an asymptomatic GI reservoir exists in humans as well, and is supported by observations of rectal CT shedding in children with trachoma and in persistently infected children after perinatal acquisition. It is thus possible that rectal shedding in asymptomatic MSM is due in part to oral acquisition, and that a similar mechanism, distinct from genital to rectal autoinoculation, may underlie the surprisingly high rectal detection in women who do not report receptive anal intercourse (16). A corollary hypothesis is that MSW who engage in oral sexual practices such as cunnilingus and anilingus with infected women may acquire and shed CT at the rectal site, where direct and autoinoculation of the rectum are unlikely; a pilot study to examine this possibility is underway. Regardless, it is clear that much needs to be learned about the biological mechanisms involved, and whether GI colonization and rectal shedding requires a different treatment approach, not only among MSM, but also among WSM.

For now, if you practice in Australia and Europe, the standard recommendation is to use doxycycline as first choice for treatment of asymptomatic rectal infection in MSM. In the

United States, until the result of the RCT is known, azithromycin and doxycycline are alternatives. A reasonable approach might include engaging the patient in the treatment decision process, favoring single dose therapy for those considered unlikely to complete a 7 day course or who prefer a single dose approach, and providing doxycycline for those who prefer what might be a more reliable therapy.

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