

ORIGINAL ARTICLE

Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

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ABSTRACT

BACKGROUND

Rectal chlamydia is a common bacterial sexually transmissible infection among men who have sex with men. Data from randomized, controlled trials are needed to guide treatment.

METHODS

In this double-blind trial conducted at five sexual health clinics in Australia, we randomly assigned men who have sex with men and who had asymptomatic rectal chlamydia to receive doxycycline (100 mg twice daily for 7 days) or azithromycin (1-g single dose). Asymptomatic chlamydia was selected as the trial focus because more than 85% of men with rectal chlamydia infection are asymptomatic, and clinical guidelines recommend a longer treatment course for symptomatic infection. The primary outcome was a negative nucleic acid amplification test for rectal chlamydia (microbiologic cure) at 4 weeks.

RESULTS

From August 2016 through August 2019, we enrolled 625 men (314 in the doxycycline group and 311 in the azithromycin group). Primary outcome data were available for 290 men (92.4%) in the doxycycline group and 297 (95.5%) in the azithromycin group. In the modified intention-to-treat population, a microbiologic cure occurred in 281 of 290 men (96.9%; 95% confidence interval [CI], 94.9 to 98.9) in the doxycycline group and in 227 of 297 (76.4%; 95% CI, 73.8 to 79.1) in the azithromycin group, for an adjusted risk difference of 19.9 percentage points (95% CI, 14.6 to 25.3; $P < 0.001$). Adverse events that included nausea, diarrhea, and vomiting were reported in 98 men (33.8%) in the doxycycline group and in 134 (45.1%) in the azithromycin group (risk difference, -11.3 percentage points; 95% CI, -19.5 to -3.2).

CONCLUSIONS

A 7-day course of doxycycline was superior to single-dose azithromycin in the treatment of rectal chlamydia infection among men who have sex with men. (Funded by the National Health and Medical Research Council; RTS Australian New Zealand Clinical Trials Registry number, ACTRN12614001125617.)

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CHLAMYDIA TRACHOMATIS IS A COMMON bacterial sexually transmitted infection (STI) globally, with an estimated 127 million cases in 2016 (the most recent year for which data are available).¹ Regular screening for rectal chlamydia is recommended for men who have sex with men,^{2,3} among whom the estimated prevalence of rectal chlamydia is approximately 9% among men attending STI clinics.⁴ There is also increasing concern about rectal chlamydia in women and its possible role in urogenital infection through autoinoculation, which increases the risk of reproductive complications associated with infection.⁵⁻⁷

Until recently, most guidelines have recommended treatment for rectal chlamydia consisting of either doxycycline (at a dose of 100 mg twice a day for 7 days) or azithromycin (in a single 1-g dose) on the assumption that both regimens were efficacious. However, a number of observations have led practitioners in several countries to change their guidelines to recommend doxycycline as first-line treatment.^{3,8} These observations include a systematic review of observational data indicating that doxycycline may be approximately 20% more efficacious than azithromycin for the treatment of rectal chlamydia,⁹ along with increasing concern about resistance to azithromycin in other STIs.¹⁰

The attraction of azithromycin for the treatment of chlamydia has been its efficacy as single-dose therapy. In the absence of a randomized, controlled trial that directly compares azithromycin with doxycycline for rectal chlamydia, any decision about changing the current guidelines could be considered premature. Therefore, we performed the double-blind, randomized, controlled Rectal Treatment Study to compare single-dose azithromycin with a 7-day course of doxycycline in a population of men who have sex with men.

METHODS

TRIAL DESIGN AND OVERSIGHT

From August 2016 through August 2019, we conducted this trial at five sexual health clinics in three Australian states (Victoria, New South Wales, and South Australia). Enrollment was limited to men with asymptomatic chlamydia because more than 85% of rectal chlamydia in-

fections among men who have sex with men are asymptomatic,¹¹ and Australian guidelines recommend a longer treatment course for symptomatic infection.³ It is recommended that men in this population should have at least annual screening for STIs.³

The trial was performed according to a protocol that has been published previously¹² and is available with the full text of this article at NEJM.org. Approval was granted by the ethics committee at Alfred Hospital. The trial was funded by the National Health and Medical Research Council and registered with the Australian New Zealand Clinical Trials Registry. The funder had no role in trial design, in the collection or analysis of the data, or in the preparation of the manuscript. Authors at the main trial center at the University of Melbourne had full access to all the data. All the authors interpreted the data and vouch for its accuracy and for the fidelity of the trial to the protocol in accordance with the CONSORT 2010 statement.¹³

PARTICIPANTS

Men were recruited when they attended the clinic for treatment within 7 days after routine screening indicated a positive diagnosis of rectal chlamydia based on nucleic acid amplification testing (NAAT) used by each clinic's provider of pathological analyses. (Details regarding screening tests are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.) Participants were eligible if they were at least 16 years of age, reported having had male-to-male sexual contact in the past 12 months, and had positive results for the presence of chlamydia on NAAT; all the participants were required to provide written informed consent in English. Men were excluded if they presented with proctitis or other anogenital symptoms, reported antibiotic use in the past 2 weeks, or had a contraindication to either trial drug.

A research nurse explained the trial to potential participants. As a protocol deviation before trial initiation, we excluded men who had received a diagnosis of concurrent syphilis, gonorrhea, or *Mycoplasma genitalium* at any infection site to minimize other antibiotic use during the trial. Asymptomatic lymphogranuloma venereum (LGV) was not detected until the end of the trial, when genotyping was performed. All the par-



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ticipants who had undergone randomization and had received a subsequent diagnosis of LGV were excluded from the analysis because LGV requires a prolonged course of doxycycline.¹⁴

RANDOMIZATION AND TREATMENT

An independent statistician created a computer-generated randomization sequence in blocks of 10, which was not stratified according to recruitment site. Staff members at an independent company prepared the trial drugs in a blinded manner and labeled them according to a prespecified sequence. All the participants and trial staff members, clinicians, and statisticians were unaware of trial-group assignments until the database lockdown and completion of the analysis.

Participants were randomly assigned in a 1:1 ratio to receive oral therapy with guideline-directed doses of either doxycycline (100 mg twice daily for 7 days) or azithromycin (single 1-g dose) (Table S2). The trial drugs were identical in appearance and packed in identical bottles. In the doxycycline group, participants took one 100-mg tablet of doxycycline and one placebo tablet with food under observation. They then received 13 tablets of doxycycline (100-mg dose) and were instructed to take a single tablet morning and night. In the azithromycin group, participants took two 500-mg tablets of azithromycin with food under observation. They then received 13 placebo tablets and were instructed to take a single tablet each morning and night. All the participants were advised to take the tablets with food and to minimize sun exposure. Participants were instructed to report any adverse events within 24 hours after the receipt of any trial drug by responding to a survey sent daily in a text message.

At recruitment, participants completed a questionnaire and provided three self-collected rectal swabs for testing, which included confirmatory testing for *C. trachomatis*, genotyping and quantification of chlamydial load, and assaying of messenger RNA (mRNA) and genomic sequencing. During the first 7 days, participants received a daily survey by text message to assess drug-related adverse events and medication adherence. At 4 weeks after recruitment, participants returned to the clinic and provided a rectal swab for test-of-cure assessment by NAAT and two additional rectal swabs (one for confirmatory testing and genotyping and one for genomic

sequencing). Participants returned their medication bottle for a pill count. Any participant who had a positive result for chlamydia on the test-of-cure assessment was retreated according to the clinical protocol.

LABORATORY AND GENETIC TESTING

Test-of-cure swabs were processed and underwent NAAT by the provider of pathological analyses for each clinic (Table S1). All other swabs were stored at -80°C at the Royal Women's Hospital, Victoria, for subsequent testing. Processing, extraction, and assay testing were performed as described in the protocol.¹² In brief, confirmatory testing used the Cobas 4800 CT/NG platform (Roche) with swab homogenate mixed with Cobas sample media at a ratio of 1:1. All samples with positive results on Cobas 4800 for *C. trachomatis* were quantified for *C. trachomatis* DNA and genotyped with the use of the gene encoding outer membrane protein A by means of quantitative polymerase-chain-reaction assays, as described previously.¹⁵

OUTCOMES

The primary efficacy outcome was a negative result on the test-of-cure NAAT for the presence of rectal chlamydia (microbiologic cure) at week 4. Secondary outcomes included reported adverse events and chlamydial load (reported as the number of DNA copies per microliter after $\log_{10}$ transformation). Investigators assessed all reported adverse events, including nausea (which was graded as mild, moderate, or severe according to the criteria of the *Medical Dictionary for Regulatory Activities*), vomiting, and diarrhea. Investigators assessed drug adherence according to the pill count if the bottle was returned; if the bottle was not returned, the assessment was based on the participant's response to a text message on day 7 or on the participant's report at the end of the trial.

STATISTICAL ANALYSIS

We determined that the enrollment of 560 participants would provide a power of 90% to detect an absolute between-group difference of 6 percentage points at a two-sided significance of 5%.⁹ We aimed to recruit 700 men (350 in each trial group) to account for a 14% loss to follow-up and a further loss of 6% for participants with LGV at recruitment.¹²

The primary outcome was evaluated in a modified intention-to-treat analysis because it excluded participants with LGV at recruitment. This population included all the participants without LGV who had undergone randomization and received testing for microbiologic cure. The per-protocol population included all the participants in the modified intention-to-treat population except those who had taken no more than 10 tablets of their assigned trial drug (which could result in a greater risk of treatment failure),¹⁶ had reported at least two episodes of diarrhea or had vomited within any 24-hour period during treatment (which could cause lower drug concentrations),¹⁷ or who had negative results on confirmatory testing for chlamydia conducted at recruitment. The aim of the per-protocol analysis was to ensure that any treatment effect was not due to nonadherence to treatment, either through not taking the trial drug or through low drug levels after vomiting or diarrhea. We compared the percentage of participants who had a microbiologic cure based on the test-of-cure NAAT results and calculated the difference in percentages and 95% confidence intervals using the treatment-group marginal average of predicted values from the logistic-regression analysis. All analyses accounted for clustering at the clinic level with the use of robust standard errors. Any important imbalances in baseline characteristics (e.g., douching before anal sex and previous chlamydia infection) and prespecified variables that were considered to be important (age and status with respect to human immunodeficiency virus [HIV] and use of HIV preexposure prophylaxis) were included in the adjustment of the primary outcome. In all the tests of the primary outcome, a two-sided P value of less than 0.05 was considered to indicate statistical significance.

Secondary analyses included an assessment of the difference in the percentages of patients who reported having adverse events and a visual presentation of chlamydial load (DNA copies per microliter of sample after $\log_{10}$ transformation) at baseline among those who had a cure or treatment failure, according to treatment group. We also performed two sensitivity analyses to investigate the effect of systematic deviations in outcomes between participants with missing outcome data and those with observed outcome data in which the deviations were specific to the

treatment groups. In one of these analyses, we assumed that all the participants with missing data in the doxycycline group had treatment failures, as compared with 50% of those in the azithromycin group; in the other, we assumed that all the participants with missing data in the azithromycin group had treatment failures, as compared with 50% of those in the doxycycline group. The per-protocol and secondary analyses were limited to point estimates of treatment effects with 95% confidence intervals. All analyses were conducted with the use of Stata software, version 16.0, according to a prespecified statistical analysis plan.¹⁸

We had two deviations from our protocol¹² or statistical analysis plan.¹⁸ In the first deviation, we did not report secondary outcomes of chlamydia reinfection and treatment failure because of bans on genomic sequencing and mRNA testing during the coronavirus disease 2019 (Covid-19) pandemic. Instead, we have provided a secondary analysis of the primary outcome that excluded the participants who were at risk for reinfection (i.e., who had condomless receptive anal sex during follow-up) and those who had a chlamydia genotype at the end of the trial that differed from the genotype identified at recruitment. In the second deviation from the protocol, we did not collect data on recent HIV viral loads and CD4+ cell counts.

RESULTS

PARTICIPANTS

Of 1035 eligible men who attended clinics during the trial period, 625 underwent randomization (314 to receive doxycycline and 311 to receive azithromycin) (Fig. 1). Age was similar among the men who participated in the trial and those who chose not to participate (32.4 years vs. 33.2 years). The characteristics of the participants were well balanced at baseline, although those in the doxycycline group were more likely to report previous chlamydia infection than were those in the azithromycin group (53.5% vs. 44.1%) and to report a higher frequency of douching before receptive anal sex (65.9% vs. 56.9%). At baseline, the chlamydial load was similar in the two groups; the presence of infection was confirmed on NAAT in 272 participants (86.6%) in the doxycycline group and in 251 (80.7%) in the azithromycin group (Table 1 and

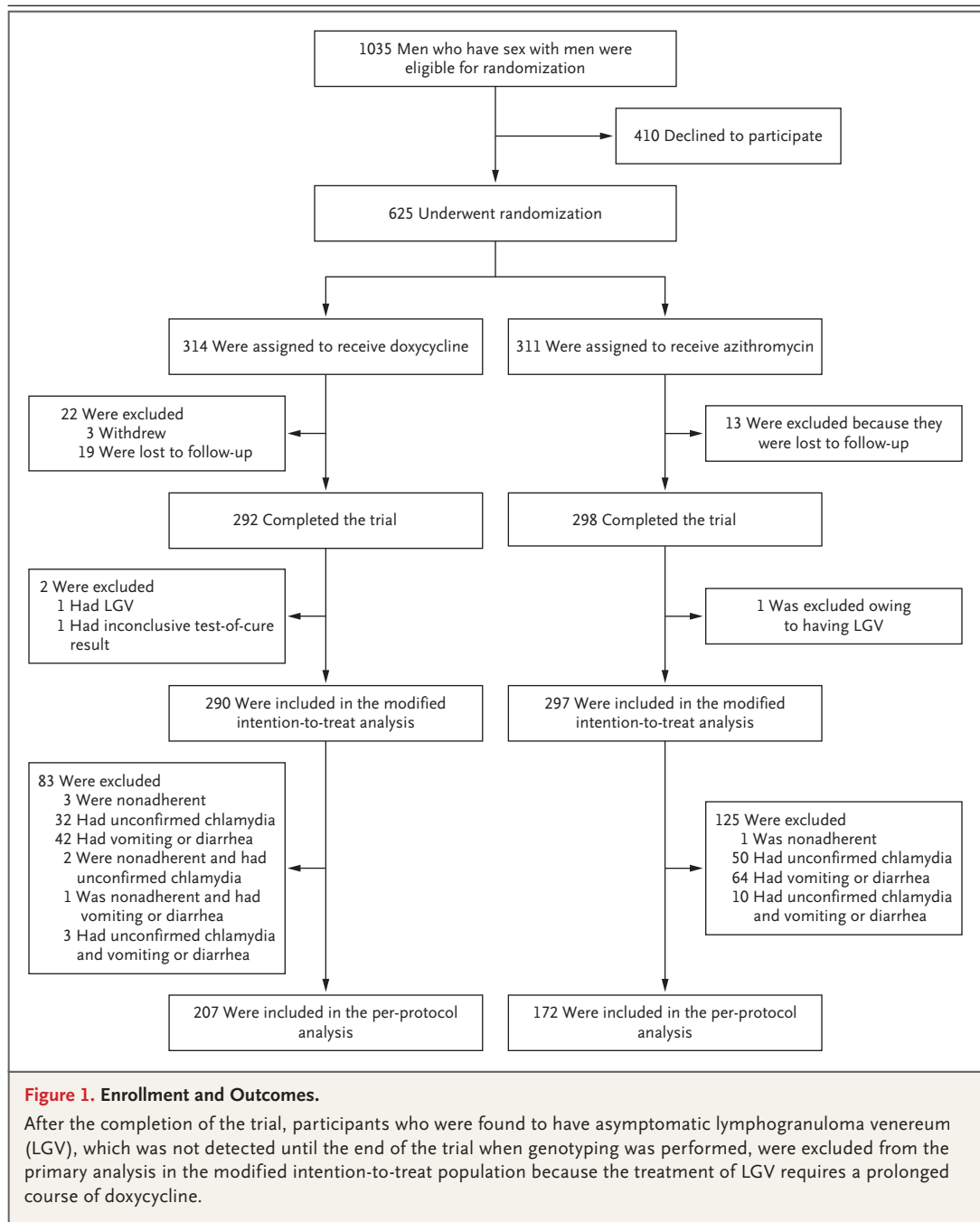


Fig. S1A). The percentage of participants with NAAT-confirmed chlamydia was similar across clinics (Table S3).

Two participants (one in each group) had LGV at baseline and were excluded. Overall, the primary analysis included 290 participants (92.4%) in the doxycycline group and 297 (95.5%) in the

azithromycin group. The duration of follow-up was similar in the two groups (Table S4).

OUTCOMES

Microbiologic cure was observed in 281 of 290 participants (96.9%) in the doxycycline group and in 227 of 297 (76.4%) in the azithromycin

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Doxycycline (N = 314)	Azithromycin (N = 311)
Age — yr	32.2±9.8	32.7±10.1
Body-mass index†	24.4±7.2	24.0±3.8
Status regarding HIV and PrEP — no. (%)		
HIV negative and PrEP negative	165 (52.5)	178 (57.2)
HIV negative and PrEP positive	106 (33.8)	107 (34.4)
HIV positive	43 (13.7)	26 (8.4)
History of STI diagnosis — no. (%)		
Chlamydia	168 (53.5)	137 (44.1)
Gonorrhea	157 (50.0)	151 (48.6)
Syphilis	72 (22.9)	63 (20.3)
Median no. of sexual partners in past 3 mo (IQR)		
Any sex	5 (3–10)	5 (3–10)
Receptive anal sex	3 (2–6)	3 (1–5)
Predominant sexual position — no./total no. (%)		
Receptive	128/308 (41.6)	131/301 (43.5)
Insertive	33/308 (10.7)	28/301 (9.3)
Both	147/308 (47.7)	142/301 (47.2)
Condom use with partners for receptive anal sex past 3 mo — no. (%)		
Never	70 (22.3)	67 (21.5)
≤50% of the time	108 (34.4)	99 (31.8)
>50% of the time	75 (23.9)	86 (27.7)
100%	51 (16.2)	41 (13.2)
No receptive anal sex in past 3 mo	10 (3.2)	18 (5.8)
Douching before receptive anal sex in past 3 mo — no. (%)		
Never	48 (15.3)	50 (16.1)
≤50% of the time	48 (15.3)	62 (19.9)
>50% of the time	207 (65.9)	177 (56.9)
Rarely had receptive anal sex in past 3 mo	11 (3.5)	22 (7.1)
Chlamydia NAAT result at recruitment — no. (%)‡		
Positive	272 (86.6)	251 (80.7)
Negative	27 (8.6)	39 (12.5)
Could not be assessed§	15 (4.8)	21 (6.8)
Chlamydial load — log ₁₀ copies per microliter	2.1±0.7	2.1±0.9

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, PrEP preexposure prophylaxis against human immunodeficiency virus (HIV), and STI sexually transmitted infection.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ This category refers to results of Cobas 4800 nucleic acid amplification testing (NAAT) of a swab that was collected at the time of recruitment for confirmatory testing.

§ Some swabs could not be assessed because of the presence of amplification inhibitors or contamination (e.g., fecal).

group, for an unadjusted risk difference of 20.5 19.9 percentage points (95% CI, 14.6 to 25.3) percentage points (95% confidence interval [CI], (P<0.001 for both comparisons) (Table 2). 16.4 to 24.6) and an adjusted risk difference of In the per-protocol population, microbiologic

Table 2. Primary Outcome.

Outcome	Doxycycline	Azithromycin	Unadjusted Risk Difference (95% CI)	P Value	Adjusted Risk Difference (95% CI)*	P Value
			<i>no./total no. (%)</i>		<i>percentage points</i>	
Microbiologic cure: negative NAAT results						
Modified intention-to-treat analysis†	281/290 (96.9)	227/297 (76.4)	20.5 (16.4–24.6)	<0.001	19.9 (14.6–25.3)	<0.001
Per-protocol analysis‡	198/207 (95.7)	126/172 (73.3)	22.4 (13.6–31.2)		21.3 (13.3–29.4)	

* Risk differences were adjusted for age, HIV status, use of HIV PrEP, douching before receptive anal sex, and history of chlamydia diagnosis.

† The primary outcome was evaluated in a modified intention-to-treat analysis because it excluded participants with lymphogranuloma venereum at recruitment. This outcome was based on a test-of-cure swab analyzed by the provider of pathological analyses for each trial site. A listing of NAAT tests that were administered at each trial site is provided in Table S1 in the Supplementary Appendix.

‡ The per-protocol population consisted of the modified intention-to-treat population with the exclusion of participants who had taken no more than 10 tablets of their assigned trial drug, who had reported at least two episodes of diarrhea or had vomited within any 24-hour period during treatment, or who had negative results on confirmatory testing for chlamydia at the time of recruitment.

cure was observed in 198 of 207 participants (95.7%) in the doxycycline group and in 126 of 172 (73.3%) in the azithromycin group, for an unadjusted risk difference of 22.4 percentage points (95% CI, 13.6 to 31.2) and an adjusted risk difference of 21.3 percentage points (95% CI, 13.3 to 29.4). Results from the secondary and sensitivity analyses were similar in direction to the results of the primary analysis (Table 2 and Tables S5 and S6).

Of the 79 participants who had treatment failure, the majority had variant G (27.9%) or D (25.3%) at baseline (Table S7). Those receiving azithromycin were more likely than those receiving doxycycline to have the same genotype at the end of the trial as the one identified at baseline (Table S8). Among the participants in the azithromycin group, the chlamydial load at baseline was greater in those with treatment failure than in those with a cure (Fig. S1B).

Adherence data were available for 260 of 290 participants (89.7%) in the doxycycline group and for 271 of 297 (91.2%) in the azithromycin group. Less than 3% of the participants in the two groups reported taking no more than 10 tablets (Table S9). Overall, the percentage of participants who guessed their assigned drug was 8.7% in the doxycycline group and 9.3% in the azithromycin group (Table S4).

ADVERSE EVENTS

Adverse events were reported in 98 of 290 participants (33.8%) in the doxycycline group and in 134 of 297 (45.1%) in the azithromycin group

(risk difference in the doxycycline group, –11.3 percentage points; 95% CI, –19.5 to –3.2) (Table 3). Similar percentages of participants in the doxycycline group and the azithromycin group reported vomiting (1.0% in each group) or nausea (21.7% and 20.5%, respectively); those receiving doxycycline were less likely to report diarrhea (25.5% vs. 39.7%; risk difference, –14.2 percentage points; 95% CI, –20.7 to –7.8). Two participants in the doxycycline group withdrew because of adverse events; neither required hospitalization.

DISCUSSION

In this randomized trial involving men who have sex with men, the doxycycline regimen was significantly more efficacious than the azithromycin regimen for the treatment of asymptomatic rectal chlamydia. The secondary and sensitivity analyses provided further support for these findings.

Our results are consistent with a 2015 review of eight observational studies showing that doxycycline was more efficacious for rectal chlamydia than azithromycin (99.6% vs. 82.9%).⁹ Subsequent observational studies have shown similar results.^{19,20} Although we could not locate any results of randomized, controlled trials, we found a conference abstract for a smaller trial involving 135 participants that showed similar results (91% cure in the doxycycline group vs. 71% in the azithromycin group).²¹

It is unclear why azithromycin is less efficacious than doxycycline for rectal chlamydia,

Table 3. Adverse Events.*

Event	Doxycycline (N=290)	Azithromycin (N=297)	Risk Difference (95% CI)	P Value
	number of participants (%)		percentage points	
Any adverse event	98 (33.8)	134 (45.1)	-11.3 (-19.5 to -3.2)	0.006
Nausea	63 (21.7)	61 (20.5)	1.2 (-3.5 to 5.8)	0.62
Mild	49 (16.9)	49 (16.5)	0.4 (-3.7 to 4.5)	0.85
Moderate	11 (3.8)	9 (3.0)	0.8 (-2.3 to 3.8)	0.63
Severe	3 (1.0)	3 (1.0)	0.0 (-1.9 to 1.8)	0.98
Vomiting	3 (1.0)	3 (1.0)	0.0 (-1.9 to 1.8)	0.98
Diarrhea	74 (25.5)	118 (39.7)	-14.2 (-20.7 to -7.8)	<0.001

* Adverse events included nausea, vomiting, or diarrhea within 24 hours after the receipt of any dose of a trial drug during the first 7 days of the trial. Grading of nausea was based on the criteria of the *Medical Dictionary for Regulatory Activities* and was reported by the participants.

since the results from other randomized, controlled trials have shown the drug to be only slightly less effective than doxycycline for urogenital infection (94% vs. 97%).²² However, a few factors may contribute to this effect.¹⁰ First, chlamydial minimal inhibitory concentration (MIC) for azithromycin is four times as high in colorectal cell lines as in endocervical cell lines, whereas the chlamydial MIC for doxycycline does not vary between cell lines.²³ Second, doxycycline is highly soluble in lipids, which facilitates a rapid distribution to infection sites; although azithromycin is also lipid soluble, the drug is transported mainly by inflammatory cells that are produced during an immune response.²⁴ Studies in animals have shown that chlamydiae in the gut are less susceptible to clearance by azithromycin than in the genital tract.²⁵ Furthermore, a study in humans showed a dampened inflammatory response to chlamydia in the rectum.²⁶ If the immune response to chlamydia is dampened in the rectum, then this may reduce azithromycin delivery to infection sites, which would reduce efficacy and explain at least in part why the drug has lower efficacy for rectal infection than for urogenital infection and lower efficacy than that of doxycycline for rectal infection.

We observed that among the participants in the azithromycin group, the chlamydial load was higher among those with treatment failure than in those who had been cured, a finding that was consistent with the results of previous studies.²⁰ This result raises the question of whether larger

azithromycin doses may be more effective for higher-load infections,¹⁰ although load data are generally unavailable at the time of the initiation of treatment.

Other evidence supports concern regarding the efficacy of azithromycin for rectal chlamydia. First, although there is little indication that azithromycin causes chlamydia resistance, the drug has been found to cause resistance in other STIs (e.g., gonorrhea, syphilis, and *M. genitalium*) that may coexist with chlamydia.²⁷ Second, rectal chlamydia in women is common, with one review showing that women with urogenital chlamydia are 30 times as likely to have concurrent rectal chlamydia as women without urogenital chlamydia.²⁸ Although azithromycin is likely to cure urogenital infection in women, it may not cure rectal chlamydia.¹⁹ This factor may be an issue if rectal chlamydia causes urogenital infection through autoinoculation.⁵ Treating urogenital chlamydia in women with doxycycline will clear rectal chlamydia, which reduces the risk of autoinoculation. Third, gastrointestinal side effects, including diarrhea, are more common with azithromycin,¹⁷ as occurred in our trial. Although there is concern about adherence with doxycycline, observational data from STI clinics suggest that a lack of adherence is unlikely to have a substantial effect on the efficacy of doxycycline.⁹ However, our results may not reflect adherence outside the strict setting of a randomized, controlled trial. Thus, azithromycin will still have a place for the treatment of chlamydia during pregnancy, when doxycycline

is not recommended, and in patients who are allergic to doxycycline.

Our trial has several limitations. First, it was limited to men. However, rectal chlamydial load is similar between the sexes,²⁹ and observational data show similar treatment efficacy in men and women,³⁰ which suggests that our findings are generalizable to women. Second, only men with asymptomatic chlamydia were eligible to participate in the trial, so the efficacy of azithromycin may be greater for symptomatic rectal infection in which there is increased inflammation.²⁴ However, randomized, controlled trials have shown that doxycycline is significantly more efficacious than azithromycin for symptomatic urogenital infection in men,²² which suggests that the same finding may apply for symptomatic rectal chlamydia. In men who have sex with men, more than 85% of cases of rectal chlamydia are asymptomatic, so our results are generalizable to the majority of cases.¹¹ Third, approximately 10% of the participants had negative results for chlamydia on confirmatory NAAT at baseline. In these participants, it is unclear whether they had spontaneous clearance of infection between initial testing at the clinic and confirmatory testing at the time of recruitment,³¹ whether the initial testing led to a false positive diagnosis, or whether the confirmatory test (which may have been less sensitive than the tests used by the clinics) led to a false negative result.³² However, the percentage of participants who had negative results for chlamydia on confirmatory testing at recruitment was similar in the two groups, and the per-protocol results were consistent with the results of the primary analysis. Fourth, we excluded men who had coinfections, so our results may not be general-

izable to these men. Finally, although our per-protocol analysis was adjusted for baseline covariates, comparing subgroups that are defined by postrandomization events can introduce potential bias.³³ However, in comparing the per-protocol results with those from the primary analysis, we did not find any evidence that treatment effects were due to either nonadherence or gastrointestinal toxicity.

Our trial provides evidence that a 7-day course of doxycycline was more efficacious than single-dose azithromycin for the treatment of asymptomatic rectal chlamydia among nearly 600 men who have sex with men.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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