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Resolution of Symptoms and Resumption of Sex After Diagnosis of Nongonococcal Urethritis Among Men Who Have Sex With Men

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Abstract

Background: Standard counseling at nongonococcal urethritis (NGU) diagnosis includes advice to abstain from sex for at least 7 days and until symptoms resolve.

Methods: From December 2014 to July 2018, we enrolled men who have sex with men and received azithromycin (1 g) for NGU at the Public Health–Seattle and King County STD Clinic. Over 12 weeks of follow-up, participants reported daily urethral symptoms and sexual activity on web-based diaries. Nongonococcal urethritis was defined as urethral symptoms or visible urethral discharge plus 5 or greater polymorphonuclear leukocytes per high-power field. Time of symptom resolution was defined as the first of 5 consecutive asymptomatic days.

Results: Of 100 participants with NGU and no *Chlamydia trachomatis* (CT)/*Mycoplasma genitalium* (MG) coinfection, 36 (36%), 22 (22%), and 42 (42%) had CT-NGU, MG-NGU, and non-CT/non-MG NGU, respectively. Among men with MG-NGU, 94% had a macrolide resistance

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mutation. For all etiologies, median time to symptom resolution after azithromycin was 7 days (95% confidence interval [CI], 5–9); 37% had symptoms lasting longer than 7 days. For men with CT-NGU, MG-NGU, and non-CT/non-MG NGU, median time to symptom resolution was 4 days (95% CI, 2–6; 16% >7 days), undefined days (95% CI, 7 to undefined; 60% >7 days), and 7 days (95% CI, 5–11; 46% >7 days), respectively. Median time to first sexual activity (any type) was 12 days (95% CI, 11–17); it was 16 days (95% CI, 12–18) to first urethral sexual exposure. Twenty-seven percent did not avoid urethral exposure for the recommended period.

Conclusions: Counseling at NGU diagnosis should educate patients that symptoms may persist more than 7 days, particularly for non-CT NGU, and emphasize the rationale for the 7-day abstinence period.

Nongonococcal urethritis (NGU) is characterized by urethral symptoms, urethral discharge, and elevated polymorphonuclear leukocytes (PMNs).¹ In the United States, patients diagnosed with NGU are generally treated presumptively with antibiotics active against *Chlamydia trachomatis* (CT), the most common bacterial cause of NGU, and advised to (1) abstain from sex for at least 7 days and until their symptoms resolve and (2) avoid sex with exposed sex partners until 7 days after those partners have been treated.² In practice, clinicians often add that, if patients are not going to abstain, they should use condoms correctly and consistently during sex. These recommendations are intended to prevent reinfection and transmission of pathogens to partners.

Time to symptom resolution after treatment is assumed to be roughly 7 days based on studies of objective evidence of clinical cure rather than patient-reported symptoms.¹ Although objective evidence is critical for defining treatment efficacy, patients' experience of symptom resolution is also important. Moreover, the timing of symptom resolution may vary by etiology and efficacy of therapy. In particular, *Mycoplasma genitalium* (MG), the second leading cause of NGU, has rapidly developed resistance to azithromycin, the common first-line presumptive NGU therapy in the United States.³ In addition, the efficacy of moxifloxacin, the recommended etiology-specific MG therapy, is declining.⁴ Finally, the frequency with which patients follow counseling advice to avoid sexual exposure while the infection clears is unknown.

An improved understanding of time to symptom resolution and adherence to behavioral recommendations would inform counseling messages, help patients know what to expect after treatment for NGU, and further our understanding of time to resolution of NGU. To address these knowledge gaps, we used daily diary data to (1) estimate time to symptom resolution and time to first urethral sexual exposure after presumptive azithromycin therapy for NGU, overall and by etiology, and (2) estimate time to symptom resolution after initiation of moxifloxacin therapy for MG-NGU, among men who have sex with men (MSM).

MATERIALS AND METHODS

Study Procedures

We enrolled Public Health–Seattle and King County Sexually Transmitted Disease Clinic patients age 16 years or older with NGU who were assigned male sex at birth and only had

sex with people assigned male sex at birth in the past year. Patients who had no sex in the past 60 days, antibiotics in the past 30 days, urethral contact to *Neisseria gonorrhoeae* (GC), no contact information, or no freezer at home to store urine specimens (not included in this analysis) were ineligible.

This cohort study included in-clinic visits every 3 weeks for 3 months, although follow-up visit data were not included in this analysis. Potentially eligible patients saw 1 of 2 study clinicians who confirmed eligibility and offered enrollment. The clinician conducted a standard clinical examination and collected first-void urine and a urethral swab specimen for Gram staining to quantitate PMNs and detect Gram-negative intracellular diplococci indicative of GC.² We defined NGU as urethral symptoms (discharge, dysuria, or other urethral symptoms) or visible urethral discharge on examination, in combination with an average of at least 5 PMNs per high-power field (HPF). Participants received presumptive treatment for NGU according to clinic standard of care during this period, which included azithromycin (1 g orally, single-dose) or doxycycline (100 mg orally twice daily, 7 days) and standard counseling.² Participants provided sociobehavioral data on a computer-assisted self-interview developed with Research Electronic Data Capture (REDCap).⁵

Urine was tested for GC and CT using the Aptima Combo 2 assay and MG using the Aptima assay with analyte-specific reagents (Hologic, Inc., Marlborough, Massachusetts). Before routine MG testing was implemented in the study in April 2016, we conducted MG testing after participants completed study follow-up. During this time, participants with persistent or recurrent NGU were treated with moxifloxacin (400 mg orally daily, 10–14 days²). We asked participants who were MG-positive at their final study visit to return for another MG test and provided moxifloxacin if positive. In April 2016, we implemented real-time MG testing (ie, conducted with GC/CT testing), and participants testing MG-positive were recalled to the clinic and provided moxifloxacin.

We retrospectively tested specimens that were MG-positive by Aptima for macrolide resistance mutations (MRM)⁶ and fluoroquinolone resistance-associated mutations in *ParC*.³ We performed DNA extraction from specimens in Aptima transport medium using a MagNA Pure 96 Instrument (Roche, Pleasanton, California) with large volume (1 mL) universal pathogen extraction protocol and elution in 50 µL. We used PCR and PyroMark Q96 sequencing to detect MRM.^{7,8} We amplified and sequenced the *parC* gene by conventional Sanger sequencing.⁹ We used quantitative PCR to estimate MG organism load.⁸

Throughout the 3-month follow-up period, participants completed weekly diaries, reporting daily instances of urethral symptoms (discharge, dysuria, pruritus, or any other unusual feeling in/on their penis), sexual behavior (including types of sex and condom use), and antibiotic therapy. We programmed and automated the diaries using REDCap, which is web-based and mobile phone-enabled. REDCap e-mailed participants a unique URL to access their diary every Monday and sent reminders every 3 days. We timed-out incomplete diaries after 7 days to ensure compliance with the recall interval. Although participants had the option to complete diaries on paper, none chose this method.

Statistical Analysis

We excluded men with CT/MG coinfection from etiology-specific analyses. We compared baseline characteristics by etiology (CT-NGU, MG-NGU, and non-CT/non-MG NGU) using Fisher exact tests and Kruskal-Wallis tests. We used the Kaplan-Meier method to estimate median time until symptom resolution after presumptive azithromycin alone; men who received additional treatment (eg, moxifloxacin) were censored at that time. Time of symptom resolution was defined as the first of 5 consecutive asymptomatic days. For participants with missing diary data before symptom resolution (12%), their symptom resolution event time was the midpoint between the first day with missing data and the first diary-day that they were known to meet our definition of symptom resolution. In bivariate analyses, we tested for between-group differences by etiology and type of urethral symptoms at enrollment using log-rank tests. We fit a Cox proportional hazards model with robust standard errors to estimate the association between NGU etiology and time to symptom resolution, adjusting for baseline confounders. We considered confounding by age (years), race/ethnicity (non-Hispanic black; non-Hispanic white; Hispanic [any race]; and other, multiple, or unknown), human immunodeficiency virus (HIV) status, HIV preexposure prophylaxis (PrEP) use, and duration (days) and type (discharge only, dysuria only, other urethral symptoms only, or >1 symptom type) of urethral symptoms. Confounders were included in the final model if they changed an exposure effect estimate by greater than 10%. Due to retrospective MG testing early in our study, we also evaluated potential effect modification by MG testing period (retrospective vs. real-time). In a separate analysis, for participants with MG-NGU during the real-time testing period and persistent urethral symptoms when they started moxifloxacin, we estimated median time until symptom resolution after initiation of moxifloxacin using the Kaplan-Meier method; men who received subsequent treatment were censored at that time. Due to uncertainty in the ideal definition of time of symptom resolution in light of intermittent symptoms, we conducted sensitivity analyses varying our definition from the first of 4 to 6 consecutive asymptomatic days.

Finally, we used the Kaplan-Meier method to estimate median time until first reported sexual activity (including any oral sex, anal sex, or rimming) and first reported urethral sexual exposure after NGU diagnosis and treatment. We defined urethral sexual exposure as insertive oral sex (IOS) or condomless insertive anal intercourse (IAI). We tested for between-group differences by etiology using a log-rank test. For participants with at least 1 day of missing diary data before their first reported urethral exposure (11%), we assumed they had no urethral exposure on missing days. We identified baseline characteristics independently associated with not following behavioral recommendations using logistic regression with robust standard errors.

This study was approved by the University of Washington Human Subjects Division. Participants provided written, informed consent. We compensated participants a total of US \$360 for their time. We used Stata 15 (StataCorp, College Station, Texas) for analyses, 2-sided tests, and significance-level $\alpha = 0.05$.

RESULTS

Between December 2014 and July 2018, we approached 502 patients about this study, of whom 204 (41%) were ineligible, 187 (37%) declined, and 111 (22%) enrolled. Most declined due to their inability to stay to enroll (21%) or attend follow-up visits (41%). Of 111 people enrolled, we excluded 8 (7%) because they received presumptive doxycycline ($n = 7$) or moxifloxacin ($n = 1$, reported contact to MG) for their NGU, and our sample size was insufficient to stratify analyses by initial therapy. The remaining 103 participants were included in baseline analyses.

Baseline Analyses

All 103 participants self-identified as cisgender men. Median age was 30 years (interquartile range [IQR], 27–39) (Table 1). Fifty-five men (53%) were non-Hispanic white, and 12 (12%) were living with HIV. Urine specimens from 36 (35%), 22 (21%), and 3 (3%) men tested positive for CT only, MG only, and both CT and MG, respectively. The remaining 42 men (41%) tested negative for both pathogens and were classified as non-CT/non-MG NGU. At enrollment, 97 men (94%) reported urethral symptoms, and 93 (90%) had visible discharge (Table 2). Most (81%) had 10 PMNs/HPF or greater. Although baseline characteristics by NGU etiology were similar, men with MG-NGU were somewhat more likely to be taking PrEP than those with CT-NGU and non-CT/non-MG NGU ($P = 0.09$).

Of 22 men with MG-NGU, 4 (18%) enrolled during the retrospective MG testing period, although none received moxifloxacin for persistent/recurrent NGU; 18 (82%) enrolled during the real-time MG testing period. Among the 17 men with MG-NGU with resistance test results, 16 (94%) had MRM and 2 (12%) had the S83I fluoroquinolone resistance-associated ParC mutation in pretreatment specimens.

Longitudinal Analyses

Ten men (10%) were excluded from longitudinal analyses because they did not report urethral symptoms at enrollment ($n = 5$) or did not have any diary data ($n = 5$). Men excluded from longitudinal analyses were younger ($P = 0.009$) and reported lower education ($P = 0.02$) than those included. The remaining 93 men in longitudinal analyses completed 89% of diaries requested, yielding diary data for a median of 86 days (IQR = 79–92).

Symptom Resolution

Twenty-one men (23%) had intermittent days (1) without urethral symptoms before meeting our definition of symptom resolution. Across all etiologies, median time to symptom resolution after presumptive azithromycin alone was 7 days (95% confidence interval [CI], 5–9) (Table 3). Among 72 men with an observed event (ie, not censored due to additional treatment or the end of their follow-up time), time to symptom resolution ranged from 1 to 39 days. Among 83 men not censored within the first 8 days, 31 (37%) had symptoms lasting more than 7 days after treatment. For men with CT-NGU, MG-NGU, and non-CT/non-MG NGU, median time to symptom resolution after azithromycin alone was 4 (95% CI, 2–6), undefined (95% CI, 7 to undefined), and 7 (95% CI, 5–11) days, respectively ($P = 0.001$) (Fig. 1). The median among men with MG-NGU was undefined because the

majority started moxifloxacin before experiencing symptom resolution. Median time to symptom resolution did not vary by type of urethral symptoms at enrollment ($P = 1.0$). Among men not censored within the first 8 days, 5 (16%), 9 (60%), and 16 (46%) had symptoms lasting more than 7 days for CT-NGU, MG-NGU, and non-CT/non-MG NGU, respectively.

Men with MG-NGU (hazard ratio [HR], 0.29; 95% CI, 0.13–0.68) and non-CT/non-MG NGU (HR, 0.56; 95% CI, 0.36–0.89) had a decreased “hazard” for symptom resolution (ie, longer time to symptom resolution) after azithromycin alone compared with those with CT-NGU (Table 4). Adjustment for baseline age, race/ethnicity, HIV status, PrEP use, duration and type of urethral symptoms, and MG testing period did not meaningfully change these estimates.

The association between MG-NGU and time to symptom resolution after azithromycin alone differed by MG testing period ($P = 0.002$). During the retrospective testing period, time to symptom resolution was shorter for men with MG-NGU compared with CT-NGU. In contrast, during the real-time testing period, time to symptom resolution was longer for men with MG-NGU than CT-NGU. However, only 4 men had MG-NGU during the retrospective testing period, and their pretreatment MG organism load was lower than that of men in the real-time testing period (median, 8 vs. 1371 genome equivalents per 5 μ L template, $P = 0.01$). When we adjusted for organism load, there was no longer a significant difference by MG testing period ($P = 0.12$).

It is important to note that of 12 men with MG-NGU during the real-time MG testing period and persistent urethral symptoms when they started moxifloxacin, 8 (89%) of 9 with resistance test results had MRM in their preazithromycin specimen. None had the S83I fluoroquinolone resistance-associated ParC mutation. Among these 12 men, median time to symptom resolution after initiation of moxifloxacin was 4 days (95% CI, 1–8). Among 11 men not censored within the first 8 days, 2 (18%) had symptoms lasting more than 7 days.

In sensitivity analyses varying our definition of time of symptom resolution from the first of 4–6 consecutive asymptomatic days, median time to symptom resolution after presumptive azithromycin alone was 6–7 days overall (34–40% >7 days) and 7–10 days for non-CT/non-MG NGU (43–47% >7 days); it remained stable for CT-NGU (4 days, 13–19% >7 days) and MG-NGU (undefined, 53–67% >7 days). Median time to symptom resolution after initiation of moxifloxacin for MG-NGU remained stable (4 days, 20–25% >7 days).

Resumption of Sex

Overall, median time to first reported sexual activity (any type) after NGU diagnosis and treatment was 12 days (95% CI, 11–17). Twenty-one men (23%) reported sex within 1 to 7 days of diagnosis. On the first day with sex, the most common behaviors reported were IOS (69%), receptive hand-penile contact (67%), condomless IAI (33%), receptive rimming (22%), and IAI with a condom (21%).

Median time to first reported urethral sexual exposure (ie IOS or condomless IAI) was longer at 16 days (95% CI, 12–18) (Table 5). Among 89 men with an observed event, time to

resumption of urethral sexual exposure ranged from 3 to 85 days. Median time to first reported urethral exposure did not differ by NGU etiology ($P=0.8$). Twenty-five men (27%) did not follow counseling advice to abstain from urethral sexual exposure for at least 7 days and until symptoms resolve. Seventeen men (18%) reported urethral exposure within 1 to 7 days, although 71% of them experienced symptom resolution before their first exposure. Overall, 13 men (14%) reported a urethral exposure before symptom resolution. Not following counseling advice was more likely in those reporting a new partner in the past 2 months (adjusted odds ratio [aOR], 8.57; 95% CI, 1.22–60.21; $P=0.03$) and less likely in those with at least 10 versus 5 to 9 PMNs/HPF (aOR, 0.26; 95% CI, 0.08–0.85; $P=0.03$) at enrollment.

DISCUSSION

Among MSM in Seattle, over 35% had urethral symptoms lasting more than 7 days after presumptive azithromycin therapy alone for NGU. Time to symptom resolution differed by NGU etiology. Symptoms lasted at least 3 days longer for men with MG-NGU and non-CT/non-MG NGU compared to CT-NGU. Among men with MG-NGU, longer time to symptom resolution after azithromycin was likely due to near universal MRM in MG. Although symptoms persisted longer for MG-NGU than CT-NGU after azithromycin alone, time to symptom resolution after starting effective therapy (ie, moxifloxacin for MG, azithromycin for CT) was similar for both etiologies (4 days). Over 25% of men did not follow counseling advice to abstain from urethral sexual exposure for at least 7 days and until symptoms resolve.

We were surprised that symptoms lasting more than 7 days after azithromycin were so common, given the high efficacy of azithromycin for non-MG NGU and prior evidence that most patients with NGU experience some or complete clinical improvement by the end of treatment.¹ Studies of tetracycline hydrochloride,¹⁰ oxytetracycline and erythromycin stearate,¹¹ minocycline,¹² and azithromycin and doxycycline^{13–16} suggest that 64% to 98% of patients experience clinical cure by 6 to 35 days after treatment initiation based on objective criteria (generally visible discharge or elevated PMNs). The studies with the shortest follow-up intervals (~6–10 days) found that 92% and 64% experienced clinical cure after minocycline¹² and tetracycline hydrochloride,¹⁰ respectively. Studies of azithromycin reported high clinical cure rates (87–94%) but after longer follow-up intervals (14–35 days), and 2 of them were conducted when MG with MRM was rare.^{13–16} It is important to note that none of these studies reported the percentage of patients with symptom resolution or the time until this occurred.

Our finding that time until symptom resolution after azithromycin varied by NGU etiology is consistent with prior evidence that the efficacy of azithromycin for achieving clinical cure is highest for CT-NGU. Among men with NGU in Seattle, 3 weeks after presumptive azithromycin therapy, clinical cure rates for men with CT, MG, and neither pathogen were 87%, 63%, and roughly 81%, respectively.¹⁶ Moreover, MRM in MG have been associated consistently with azithromycin treatment failure.³ Thus, the 94% prevalence of MRM among men with MG-NGU in our study likely contributed to their long duration of symptoms after azithromycin (60% symptomatic >7 days). In contrast, symptom resolution occurred

relatively rapidly after initiation of moxifloxacin for MG (18% symptomatic >7 days). Although we were surprised that median time to symptom resolution was shorter for the 4 men with MG-NGU enrolled during the retrospective MG testing period (none treated with moxifloxacin) than the 14 enrolled during the real-time testing period (all treated with moxifloxacin), this appeared to be explained by very low MG organism load in the initial 4 men. Inadequate treatment of unidentified pathogens or polymicrobial communities may have contributed to the long duration of symptoms for men with non-CT/non-MG NGU.

To our knowledge, adherence to counseling advice on sexual abstinence immediately after NGU diagnosis has not been evaluated previously. We found that 23% of men resumed sexual activity during the recommended 7-day abstinence period, 81% of whom reported urethral sexual exposures, although many of these men waited for their symptoms to resolve first. The implications of this for transmission of pathogens to partners depend on how long it takes men to clear NGU-associated pathogens after treatment and how well this correlates with symptom resolution. Although we could not evaluate clinical or microbiologic cure until 21 days after initiation of treatment, a prior study of CT clearance in women found that 3, 7, 10, and 14 days after azithromycin 1 g treatment 88%, 54%, 34%, and 21% of women, respectively, still had detectable CT ribosomal ribonucleic acid.¹⁷ However, the extent to which these nucleic acids represent viable organisms is uncertain. MG likely clears more quickly than CT when effective treatment is provided. Among men and women with macrolide-susceptible MG infection, 38% and 4% had detectable MG nucleic acids 6 and 8 days, respectively, after azithromycin 1.5 g treatment; none had detectable nucleic acids 3 days after starting moxifloxacin.¹⁸ However, we expect MG clearance to depend on the prevalence of antimicrobial resistance.³ Nonetheless, the anti-inflammatory properties of azithromycin^{19,20} may lead to symptom resolution before pathogen clearance, suggesting that a recommended abstinence period is critical irrespective of symptom resolution. Currently, United States, Australian, European, and Canadian NGU management guidelines all emphasize a 7-day abstinence period.^{2,21–23}

Our analysis has limitations. There was no precedent for defining time of symptom resolution with daily data, and 23% of our participants reported intermittent symptoms. Our definition (the first of 5 consecutive asymptomatic days) was intended to capture the subjective threshold at which intermittent symptoms would be considered persistent rather than recurrent clinically. Varying this definition from the first of 4 to 6 consecutive asymptomatic days did not meaningfully change our findings. Nonetheless, our definition likely differs from that of patients, who may consider it “safe” to resume sex on the first symptomless day. Additionally, we did not consider objective evidence of clinical or microbiologic cure in this analysis. Some men with prompt symptom resolution may have had persistent urethral inflammation or infection. Similarly, some men with a long duration of symptoms may have experienced rapid pathogen clearance. Nevertheless, understanding the patient experience of symptom resolution is an important aspect of clinical care. This analysis did not consider recurrent symptoms after initial resolution, and recurrent NGU is common.¹ Moreover, we did not have information on sex partner treatment with which to evaluate that aspect of clinical counseling. Furthermore, younger men were slightly under-represented in the longitudinal analyses. Symptoms may resolve slower for younger patients who have had no or fewer prior cases of NGU. Finally, the true event times for some men

were uncertain due to missing diary data, some of which may reflect an un-willingness to admit to non-compliance with counseling guidance. For our time to symptom resolution analysis, we also fit a proportional hazards model with interval censoring, and our estimates remained stable. For our time to resumption of sex analysis, we assumed men had no urethral sexual exposure on missing days, so we likely over-estimated the true time to first exposure. Moreover, some men who had sex with condoms during the recommended abstinence period may have used the condom incorrectly or inconsistently, leading to urethral exposure and further over-estimating the true time to first exposure.

Among MSM in Seattle, NGU symptoms often persisted for more than 7 days after presumptive azithromycin alone for NGU, particularly in those with MG-NGU or non-CT/non-MG NGU. Only 40% of men with MG-NGU and 54% of men with non-CT/non-MG NGU would be expected to experience symptom resolution within 7 days of azithromycin alone. Rapid treatment of MG-positive men with moxifloxacin may improve this for some but is dependent on access to testing. Given this, and our observation that over 1-in-4 men did not follow counseling advice, standard counseling at NGU diagnosis should educate patients that symptoms may persist for more than 7 days, but will likely still resolve, and emphasize the importance of the 7-day abstinence period for prevention of ongoing transmission.

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Figure 1.

Time to symptom resolution after presumptive azithromycin therapy alone for NGU among MSM, by etiology*[†].

*Among men with urethral symptoms at enrollment (n = 5 excluded), with some diary data (n = 5 additional excluded), and who were not coinfectd with CT and MG (n = 2 additional excluded). [†]Time of symptom resolution defined as the first of 5 consecutive asymptomatic days.

TABLE 1.

Baseline Characteristics of MSM With NGU, Overall and by Etiology

Characteristics*	Overall (N = 103), n (%)	CT-NGU [†] (n = 36), n (%)	MG-NGU [†] (n = 22), n (%)	Non-CT/non-MG NGU (n = 42), n (%)	P [‡]
Age, median (IQR)	30 (27–39)	31 (27–37)	31 (28–40)	30 (27–40)	0.782 [§]
Race/ethnicity					0.157
Non-Hispanic black	7(7)	4(11)	0(0)	3(7)	
Non-Hispanic white	55 (53)	18 (50)	12 (55)	23 (55)	
Hispanic (any race)	19(19)	5(14)	2(9)	11 (26)	
Other, multiple, or unknown	22(21)	9 (25)	8(36)	5(12)	
Education completed					0.306
High school or GED	25 (25)	12 (34)	5 (23)	7(17)	
Some college	28 (27)	6(17)	6 (27)	15 (36)	
College graduate	49 (48)	17 (49)	11 (50)	20 (47)	
Known HIV-positive	12(12)	6(17)	3(14)	3 (7)	0.383
HIV PrEP use [¶]	18(20)	5(17)	7 (37)	5(13)	0.092
History of previous STD					
History of NGU	37 (36)	12 (33)	9(41)	15 (36)	0.831
History of GC infection	58 (56)	20 (56)	15 (68)	21 (50)	0.391
History of CT infection	60 (58)	22 (61)	14 (64)	22 (53)	0.633
Lifetime number of sex partners					0.573
1–9	5(5)	1(3)	1(5)	3 (8)	
10–49	29 (29)	12 (34)	5 (23)	12(31)	
50–99	24 (24)	11 (31)	6 (27)	6(15)	
100	41 (42)	11 (31)	10 (45)	18 (46)	
No. sex partners in the past 2 months, median (IQR)					
Any type of sex	3 (2–6)	3 (2–5)	4 (3–7)	3 (2–6)	0.253 [§]
IAI	2 (1–4)	2(1–4)	2 (2–5)	2(1–4)	0.814 [§]
Receptive anal intercourse	1 (0–2)	1 (0–2)	1.5 (1–2)	1 (0–2)	0.101 [§]
IOS	3 (2–5)	2.5 (2–5)	4 (3–6)	3 (2–5)	0.387 [§]

Characteristics [*]	Overall (N = 103), n (%)	CT-NGU [†] (n = 36), n (%)	MG-NGU [‡] (n = 22), n (%)	Non-CT/non-MG NGU (n = 42), n (%)	P [§]
New sex partner in the past 2 months	83 (81)	28 (78)	19 (86)	34 (81)	0.719

GED, General Education Diploma; STD, sexually transmitted disease.

^{*} n = 1 missing education completed, n = 4 missing lifetime number of sex partners, n = 3 missing number sex partners past 2 months, n = 3 missing number IAI partners past 2 months, n = 1 missing number of receptive anal intercourse partners past 2 months, and n = 1 missing number of IOS partners past 2 months.

[†] Excludes men coinfecting with CT and MG (n = 3).

[‡] Fisher's exact test unless otherwise specified.

[§] Kruskal-Wallis test.

// Among men not known to be HIV-positive (n = 91 overall, n = 30 CT-NGU, n = 19 MG-NGU, n = 39 non-CT/non-MG NGU).

TABLE 2.

Baseline Clinical Presentation of NGU Among MSM, Overall and by Etiology

Characteristics	Overall (N = 103), n (%)	CT-NGU* (n = 36), n (%)	MG-NGU* (n = 22), n (%)	Non-CT/non-MG NGU (n = 42), n (%)	P [†]
Urethral symptoms	97 (94)	35 (97)	21 (95)	39 (93)	0.841
Type(s)					
Urethral discharge	51 (53)	18(51)	12 (57)	20 (51)	0.930
Dysuria	62 (64)	22 (63)	16(76)	23 (59)	0.410
Other urethral symptoms	54 (56)	21 (60)	8 (38)	24 (62)	0.206
Duration: median (IQR), [‡] d	4 (2–9)	4.5 (2–9)	2.5 (2–10)	4.5 (2.5–7)	0.744 [§]
Visible urethral discharge	93 (90)	34 (94)	20 (91)	36 (86)	0.429
Character					0.308
Clear	61 (66)	25 (74)	12 (60)	22 (61)	
Cloudy	25 (27)	9(26)	6(30)	10(28)	
Mucoid or purulent	7(7)	0 (0)	2(10)	4(11)	
Amount					0.916
Small	57 (61)	22 (65)	12 (60)	20 (56)	
Moderate	34 (37)	11 (32)	8 (40)	15(42)	
Large	2(2)	1 (3)	0 (0)	1(3)	
PMNs/HPF on a urethral Gram stain					0.163
5–9	20 (19)	4(11)	7 (32)	8(19)	
10	83 (81)	32 (89)	15 (68)	34 (81)	
MRM in MG [¶]	—	—	16 (94)	—	—
S83I fluoroquinolone resistance-associated ParC mutation in MG [¶]	—	—	2(12)	—	—
MG organism load (genome equivalents/5 µL template), median (IQR) [¶]			403 (11–2,230)		

* Excludes men coinfected with CT and MG (n = 3).

[†] Fisher's exact test unless otherwise indicated.[‡] Missing for n = 2 who reported unknown or sporadic duration of urethral symptoms.[§] Kruskal-Wallis test.

// n = 5 with MG-NGU missing data on resistance-associated mutations and MG organism load.

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TABLE 3.

Time to Symptom Resolution by Treatment Type Among MSM With NGU, Overall and by Etiology^{*,†}

	Etiology	Median (95% CI), d	P [‡]	>7 days, Among Men Not Censored Within the First 8 Days, [§] n (%)
After presumptive azithromycin therapy for NGU	Overall (n = 93)	7 (5–9)	—	31 (37)
	By etiology			
	CT-NGU (n = 32)	4 (2–6)		5 (16)
	MG-NGU (n = 22)	undefined (7-undefined)	0.001	9 (60)
	Non-CT/non-MG (n = 37)	7 (5–11)		16 (46)
After initiation of moxifloxacin therapy for MG	MG-NGU (n = 12) [¶]	4 (1–8)	—	2 (18)

^{*} Among men with urethral symptoms at enrollment (n = 5 excluded) and some diary data (n = 5 additional excluded).[†] Time of symptom resolution defined as the first of 5 consecutive asymptomatic days.[‡] Log-rank test.[§] Among men not censored within the first 8 days for the azithromycin analysis (excludes n = 10 overall, n = 7 MG-NGU, n = 2 non-CT/non-MG NGU) and moxifloxacin analysis (excludes n = 1).^{||} Excludes men coinfecting with CT and MG (n = 2).[¶] Among men with MG-NGU during the real-time testing period (n = 4 excluded) known to have persistent urethral symptoms when they started moxifloxacin (n = 6 additional excluded).

TABLE 4.

Cox Proportional Hazards Model to Estimate the Association Between NGU Etiology and Time to Symptom Resolution After Presumptive Azithromycin Therapy Alone for NGU Among MSM^{*†}

Etiology	HR (95% CI) [‡]	P
CT-NGU (n = 32)	Reference	
MG-NGU (n = 22)	0.29 (0.13–0.68)	0.004
Non-CT/non-MG (n = 37)	0.56 (0.36–0.89)	0.013

* Among men with urethral symptoms at enrollment (n = 5 excluded), with some diary data (n = 5 additional excluded), and not coinfecting with CT and MG (n = 2 additional excluded).

† Time of symptom resolution defined as the first of 5 consecutive asymptomatic days.

‡ Adjustment for age (years), race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic [any race], other/multiple/unknown), known HIV-positive status, PrEP use at enrollment, duration of urethral symptoms before enrollment (days), type of urethral symptoms at enrollment (discharge only, dysuria only, other urethral symptoms only, >1 symptom), and MG testing period (retrospective vs. real-time) did not change these estimates by >10%.

TABLE 5.

Time to First Known Urethral Sexual Exposure After Presumptive Azithromycin Therapy for NGU Among MSM, Overall and by Etiology^{*,†}

Etiology	Median (95% CI), d	P [‡]	>7 days, Among Men not Censored Within the First 7 Days, § n (%)
Overall (n = 93)	16(12–18)		75 (82)
By etiology			
CT-NGU (n = 32)	14(10–23)		28 (88)
MG-NGU (n = 22)	14(8–22)	0.753	17 (77)
Non-CT/non-MG NGU (n = 37)	17(10–22)		28 (78)

* Among men with urethral symptoms at enrollment (n = 5 excluded) and some diary data (n = 5 additional excluded).

† Urethral sexual exposure defined as any IOS or condomless IAI.

‡ Log-rank test.

§ Among men not censored within the first 7 days (excludes n = 1 overall, n = 1 non-CT/non-MG NGU).

|| Excludes men coinfecting with CT and MG (n = 2).