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Demographic, Behavioral, and Clinical Characteristics of Men With Nongonococcal Urethritis Differ by Etiology: A Case-Comparison Study

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Abstract

Background—Nongonococcal urethritis (NGU) is common, yet up to 50% of cases have no defined etiology. The extent to which risk profiles and clinical presentations of pathogen-associated and idiopathic cases differ is largely unknown.

Methods—Urethral swabs and urine specimens were collected from 370 NGU treatment trial participants who sought care at a sexually transmitted disease clinic in Seattle, WA from 2007 to 2009 and had a visible urethral discharge and/or microscopic evidence of urethral inflammation assessed by Gram-stain (≥ 5 polymorphonuclear leukocytes per high-powered field [PMNs/HPF]). *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Trichomonas vaginalis* (TV), and *Ureaplasma urealyticum* (UU) were detected in urine, using nucleic acid amplification tests. Cases negative for all assessed pathogens were considered idiopathic. Bivariate and multivariate analyses identified clinical, sociodemographic, and behavioral factors associated with detection of specific pathogens.

Results—After excluding 3 participants with gonococcal infection, pathogens were detected in only 50.7% of the 367 eligible cases: CT in 22.3%, MG in 12.5%, TV in 2.5%, and UU in 24.0%, with multiple pathogens detected in 9.5%. In all, 3.5% of cases were negative for CT, MG, and TV but lacked speciated ureaplasma results. The remaining cases (45.8%) were considered idiopathic. Pathogen detection was associated with young age, black race, risky sexual behaviors, cloudy or purulent discharge, and visible discharge plus ≥ 5 PMNs/HPF. In contrast, idiopathic

cases were more likely to report prior NGU, were older and less likely to be black, or have an abnormal urethral discharge on examination, compared to all other cases. These cases were not associated with any high risk behaviors.

Conclusions—NGU is a heterogeneous condition. Pathogen detection was associated with a variety of traditional risk factors and clinical features; whereas, idiopathic cases tended to be diagnosed among lower-risk men.

Nongonococcal urethritis (NGU) is the most common male reproductive tract syndrome¹ and is associated with infection with *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Trichomonas vaginalis* (TV), and occasionally herpes simplex virus, and adenovirus.² Several recent studies of the newly differentiated ureaplasma species, *Ureaplasma urealyticum* (UU) and *Ureaplasma parvum* (UP), suggest a possible causal role for UU, but not UP, with this syndrome.^{3–6} Still, no potential etiologic agents have been identified in as many as 50% of NGU cases² and these idiopathic urethritis cases could be due to either unidentified sexually transmitted pathogens or noninfectious causes.⁷ Since risk factors for and clinical features of NGU may vary by etiology,^{7,8} prevention and treatment efforts could be more effectively targeted if this heterogeneity was better understood. To this end, we explored the demographic, behavioral, and clinical characteristics of men with NGU, with and without pathogens detected.

MATERIALS AND METHODS

Study Population

Between May 2007 and October 2009, 370 male sexually transmitted disease (STD) clinic patients entered a treatment trial for NGU in Seattle, WA. All participants presented with a visible urethral discharge or ≥ 5 polymorphonuclear leukocytes (PMNs) per high-powered field (HPF) (1000 $\times$) averaged over ≥ 3 fields (hereafter, abbreviated “ ≥ 5 PMNs/HPF”) on a urethral Gram-stained smear, in the absence of Gram-negative intracellular diplococci indicative of gonococcal infection.⁹ Men who had used antibiotics in the past month were not eligible. Three men with gonococcal infections detected by urine assay after enrollment and randomization were excluded from the study, yielding a final sample size of 367 NGU cases.

Data Collection

A single research clinician (M.S.L.) performed all physical examinations. Two urethral swab specimens were obtained. The first was used to prepare a Gram-stained smear; the second was stored at -70°C for future testing. The Gram-stained smear was examined by microscopy and the number of PMNs per HPF averaged over ≥ 3 fields was classified as “0 to 4,” “5 to 9,” and “ ≥ 10 ” on the clinic chart. Participants then provided a 25 to 30 mL sample of first-void urine, which was tested for *Neisseria gonorrhoeae* and CT using APTIMA Combo 2 assay (Gen-Probe Inc., San Diego, CA), TV using research-use only APTIMA TV analyte-specific reagents (Gen-Probe Inc., San Diego, CA),¹⁰ MG using our in-house polymerase chain reaction (PCR),¹¹ and ureaplasmas by culture following 1 week incubation in U broth.¹² An additional aliquot of urine was frozen at -70°C and later used to reculture ureaplasmas in batches, which were subsequently speciated using our in-house

UU- and UP-specific PCR assays.^{13,14} Urea-plasma cultures were not available for speciation procedures for 8 men (1 CT-positive case and 7 CT/MG/TV-negative cases). Another 9 men (3 CT-positive cases and 6 CT/MG/TV-negative cases) had positive ureaplasma cultures but negative ureaplasma species-specific PCR results and were considered as ureaplasma-positive but unspciated. Although these 17 men without speciated ureaplasma results were included in analyses of CT, MG, and TV, they were excluded from analyses of UU. Similarly, 3 men with inhibited MG PCR results (2 CT-positive cases and 1 TV/UU-positive case) were retained in analyses of the other pathogens, but excluded from analyses of MG.

All CT-MG-TV-UU-negative cases ($n = 168$), including those who tested positive for UP ($n = 32$), were considered idiopathic. CT-MG-TV-negative cases without confirmed speciated ureaplasma results (because cultures were not available for speciation procedures [$n = 7$] or neither ureaplasma species was identified by PCR from the positive culture [$n = 6$]) were not considered to be idiopathic because UU infection could not be ruled out. These cases were excluded from analyses of UU and idiopathic urethritis.

Symptom data, clinical history, and sociodemographic and behavioral characteristics were collected by clinician interview and computer-assisted self-interview. The duration of symptoms beginning on the day of the clinic visit was considered to be 0.5 days; values for all other durations were the number of days stated. Some participants were not asked about characteristics of sexual partners within the previous 2 months ($n = 9$) or history of depression ($n = 160$) due to questionnaire revisions after enrollment began.

Statistical Analyses

For exploratory analyses, Pearson chi-squared tests and 2 sample t tests identified factors associated with detection of the organisms of interest. Fisher exact tests and Wilcoxon rank sum tests were used when expected cell counts were ≤ 5 or data were nonnormally distributed. To identify distinguishing characteristics of men with NGU that might suggest infection with a specific pathogen, bivariate analyses included all men, even those who were coinfecting with multiple pathogens. In each pathogen-specific bivariate analysis, men testing positive for the specified pathogen were compared with those testing negative for the specified pathogen. We used multivariable Poisson regression with a log link and robust standard errors to estimate relative risks because pathogen detection among our study population of men with NGU was common.¹⁵ We identified factors independently associated with specific pathogens after adjusting for age, race, and coinfection with any other pathogens, by comparing all positive cases to all negative cases in pathogen-specific models for CT, MG, and UU (e.g., CT-positive cases were compared to CT-negative cases in 1 multivariable model, while MG-positive cases were compared to MG-negative cases in a separate multivariable model). A similar approach was used to evaluate independent correlates of idiopathic urethritis, with men testing positive for any urethral pathogen serving as the referent group. To assess the impact of our treatment trial case definition on study findings, we evaluated our multivariable models first among all study participants ($n = 367$), including asymptomatic men enrolled on the basis of a visible discharge alone ($n = 12$) or ≥ 5 PMNs/HPF alone ($n = 13$), and also among the subset of cases who met a more

restrictive case definition: symptoms or signs consistent with urethritis (complaints of discharge, dysuria, or visible discharge on examination) in addition to microscopic evidence of urethral inflammation (≥ 5 PMNs/HPF) ($n = 307$). Data were too sparse to evaluate correlates of TV infection in multivariable models, and associations with history of depression and characteristics of sexual partners from the previous 2 months were only evaluated bivariately because these data were not available for a substantial proportion of study participants. Analyses were performed using STATA statistical software (Version 11.0; StataCorp, College Station, TX). Two-sided tests were used, and the level of significance was set at $P = 0.05$.

RESULTS

A total of 367 men without gonococcal infection were enrolled and evaluated for sociodemographic, behavioral, and clinical characteristics (Table 1). Mean age was 33.9 years (range, 17.0–62.3). Most described themselves as white (52.0%) or black (35.4%), 4.1% reported Hispanic ethnicity. A prior history of STD was reported by 64.3%, 28.9% reported any male sex partners in the previous 12 months, and 83.0% were circumcised. Overall, 69.2% reported symptoms of urethral discharge or dysuria, and as per treatment trial inclusion criteria, all men had either a visible discharge (89.7%) or ≥ 5 PMNs/HPF on the urethral Gram-stain (89.7%). Most (79.3%) satisfied both study eligibility criteria.

Known urethral pathogens were detected in only 50.7% of men: CT in 22.3%, MG in 12.5%, TV in 2.5%, and UU in 24.0%, with multiple pathogens detected in 9.5% of all participants. As 3.5% of cases were negative for CT, MG, and TV, but lacked speciated ureaplasma results, the remaining 45.8% of cases were considered idiopathic. UP, which was not considered a urethral pathogen in these analyses, was detected in 13.6% of men (36.0% of whom also had at least 1 urethral pathogen detected).

Distinct demographic profiles emerged when NGU cases were stratified by organisms detected. Although TV-positive and idiopathic cases were significantly older than other cases in univariate analyses ($P = 0.01$ and $P = 0.003$, respectively), CT-positive and MG-positive men were significantly younger ($P = 0.004$ and $P = 0.008$, respectively). Men with MG, TV, and UU were significantly more likely to report black race compared to other men ($P = 0.03$, $P < 0.001$, and $P < 0.001$, respectively). In contrast, idiopathic cases were significantly less likely to report black race ($P = 0.001$), no education beyond high school ($P = 0.008$), or $< \$10,000$ annual income ($P = 0.03$).

About sexual behaviors and partner characteristics, CT-positive men were more likely than other cases to report sex with men ($P = 0.001$). In contrast, compared with all other cases, UU-positive men were significantly less likely to report sex with men ($P = 0.005$). None of the TV-positive cases reported having sex with men, although numbers were small and findings were not statistically significant ($P = 0.1$). The most recent female partners of TV-positive men were significantly older than the partners of TV-negative cases ($P = 0.03$), and significantly longer partnerships were reported compared to other cases ($P = 0.04$). MG-positive men were more likely to report ever having received money for sex ($P = 0.02$) and to classify their most recent partner as black ($P = 0.007$), compared to other cases. Finally,

men with idiopathic urethritis reported significantly fewer sex partners in the past 2 months ($P = 0.05$), compared to other cases. No other sexual behaviors were associated with this condition.

Symptoms reported by NGU cases also differed somewhat by etiology. CT-positive men reported significantly more days of urethral discharge or dysuria before the clinic visit ($P = 0.01$ and $P = 0.004$, respectively), and MG-positive cases were more likely to complain of discharge ($P = 0.03$), compared to other cases. Idiopathic cases were significantly less likely to complain of discharge, dysuria, or itching ($P = 0.03$, $P = 0.02$, and $P = 0.005$, respectively), and those with discharge or dysuria reported significantly fewer days of these symptoms before the clinic visit than other cases ($P = 0.007$ and $P = 0.01$, respectively). Also, CT-positive cases were significantly less likely to report a history of NGU ($P = 0.002$), while idiopathic cases were significantly more likely to report histories of NGU ($P = 0.004$) and diagnosis of depression ($P = 0.01$). Detection of TV or UU was not associated with any symptoms or medical history.

Several differences by etiology were detected during the clinical assessment, though the magnitude of most of these differences was small. Men in whom CT was detected were significantly more likely to have ≥ 5 PMNs/HPF in urethral exudates than other cases ($P = 0.001$), while microscopic evidence of inflammation was not significantly associated with MG detection ($P = 0.2$). CT-positive and MG-positive men were significantly more likely to satisfy both components of the treatment trial case definition (visible discharge on examination and ≥ 5 PMNs/HPF), compared to other cases ($P = 0.001$ and $P = 0.03$, respectively). CT-positive men were also significantly more likely to have ≥ 10 PMNs/HPF ($P = 0.03$). In contrast, men with idiopathic urethritis were less likely to have ≥ 5 PMNs/HPF ($P = 0.003$) and therefore a smaller proportion of these cases satisfied both components of the treatment trial case definition ($P = 0.001$). While MG-positive and UU-positive cases were significantly more likely to have cloudy or purulent discharge noted (vs. none or clear discharge) ($P = 0.05$ and $P = 0.002$, respectively), idiopathic cases were significantly less likely to have these signs ($P = 0.001$), compared to other cases.

TV-positive men were significantly more likely to have a UU coinfection compared to other cases ($P = 0.02$) (and vice versa [$P = 0.03$]). In contrast, CT-positive men were significantly less likely to have any other organisms detected ($P = 0.004$).

Multivariable analyses identified distinct profiles of demographic characteristics, behaviors, complaints, histories, and examination findings independently associated with CT, MG and UU detection among men with NGU, after adjusting for detection of other organisms (Table 2). Among men with NGU, CT detection was independently associated with young age, having a male sex partner, and having a visible discharge on examination in addition to microscopic evidence of inflammation. Such men were also significantly less likely to report a history of NGU or have any other pathogen detected, and somewhat more likely to be black. Further adjustment for time since voiding had no effect and was excluded from the model. MG detection was associated with young age, black race, ever having received money for sex, and complaints of urethral discharge. MG detection was not associated with detection of another pathogen. UU detection was not associated with age, race, or detection

of other pathogens, but was associated with less education, having 1 female sex partner in the previous 2 months, and presence of cloudy or purulent urethral discharge.

In contrast to factors associated with pathogen detection, black race, complaints of penile itching, presence of cloudy or purulent urethral discharge, and having both visible discharge on examination and microscopic evidence of inflammation were inversely associated with idiopathic urethritis. These men were significantly older than cases with pathogens detected, and were significantly more likely to report a history of NGU.

Findings for all multivariable models were similar in sensitivity analyses when the study population was restricted to men with symptoms or signs consistent with urethritis in addition to microscopic evidence of urethral inflammation (data not shown).

DISCUSSION

We sought to identify characteristics of men with NGU that could distinguish men infected with specific pathogens from other cases. In addition to CT, which was associated with more than 20% of cases in this analysis, we assessed infection with MG and TV, recognized nonviral pathogens that are not part of the standard clinical work-up for NGU, and UU, a suspected etiologic agent of NGU. These other pathogens, for which routine testing is not performed, were found in one-third of cases enrolled in our study. Despite this extensive testing, approximately 50% of cases were idiopathic, which is consistent with previous estimates.²

Cases clustered into distinct profiles when stratified by etiology. In multivariable models, pathogen detection among NGU cases was associated with traditional sexually transmitted infection (STI) risk factors, such as young age, black race, and risky sexual behaviors, and clinical features consistent with urethral inflammation due to infectious etiology (i.e., abnormal discharge, and visible discharge in addition to microscopic evidence of inflammation). In contrast, idiopathic urethritis was not associated with any risk behaviors, and this condition was inversely associated with young age and black race. Furthermore, idiopathic urethritis was distinguished by less frequent symptoms (i.e., penile itch) or clinical findings (i.e., cloudy/purulent discharge or any visible discharge in addition to microscopic evidence of inflammation). While the association between prior history of NGU and idiopathic urethritis could suggest persistent or recurrent infection with unrecognized organisms among these men, it could also suggest unresolved urethral inflammation due to noninfectious causes. Symptomatic idiopathic cases reported significantly fewer days of discharge or dysuria before the clinic visit than pathogen-positive cases in bivariate analyses, which could indicate greater symptom severity among these men. However, the associations with shorter durations of symptoms did not persist in multivariable analyses after adjusting for age, race, and history of NGU, suggesting that older men, white men, or those with a history of NGU might recognize symptoms faster, be more likely to seek care for recognized symptoms, and/or might have better access to clinical care.

Our findings are largely consistent with those of 2 previous case-comparison studies. Like us, Varela et al observed associations between chlamydial urethritis and having male sex

partners, between undifferentiated ureaplasmas and having female sex partners, and between TV detection and older age in a comparison of men with ≥ 5 PMNs/HPF presenting to Spanish STD clinics.⁷ Also consistent with our findings, Bradshaw et al found that CT-positive Australian men reporting acute symptoms of urethritis tended to be younger than CT-negative men with urethral symptoms and that “pathogen negative” symptomatic men were older than those with any pathogens detected.⁸ In contrast with our findings, MG-positive men with urethral symptoms were significantly older than MG-negative symptomatic men in the Australian cohort. Bradshaw et al also found that microscopic evidence of inflammation was more common among symptomatic men with CT or MG detected, and that “pathogen negative” men were significantly more likely to have no or “normal” urethral discharge compared to other men with urethral symptoms, which is consistent with data from our cohort of men with NGU.

These analyses were designed to help clinicians distinguish between pathogens in the absence of rapid point-of-care diagnostic tests, or commercially available tests for organisms such as MG and differentiated UU; yet they raise numerous questions about clinical management. Men with NGU are usually treated empirically before test results are available. However, most trials of therapies for NGU have been designed with resolution of chlamydial infection as the end point,¹⁶ which was responsible for only 22% of cases in this study. Trials assessing the response of MG to these therapies are only now beginning to emerge¹⁷ and none to date have evaluated whether there is differential response to therapy by the 2 *Ureaplasma* species. Idiopathic urethritis represented a high proportion of cases (45.8%) here and was typified by low-risk characteristics in this population, suggesting that this condition may not have an infectious etiology, or may be due to unidentified infectious agents circulating in subgroups of the population different from those infected with traditional STI pathogens. Data on the response of idiopathic urethritis cases to Centers for Disease Control and Prevention-recommended therapies are limited and difficult to interpret, but if a sizeable proportion is not due to infectious agents, it will be important to learn how to distinguish noninfectious cases and exclude them from the prescription of therapy for NGU and partner management efforts. Whether it is time to begin routinely testing men with NGU for MG remains a matter of debate and an unresolved question.^{17,18}

This comprehensive comparison of NGU cases by etiology highlights important differences in sociodemographic, behavioral, and clinical factors. Although we assessed infection with numerous pathogens using sensitive nucleic acid amplification tests, our testing was not exhaustive, as we could not routinely assay for herpes simplex virus or adenovirus, which may explain some of our idiopathic cases. Because the goal of this study was to determine if any characteristics evaluated during the routine clinical assessment could be used to distinguish NGU cases by etiology, we performed a case-comparison analysis rather than a case-control study. Multivariable modeling allowed us to assess factors independently associated with pathogens involved in clinically confirmed urethritis, as well as idiopathic urethritis. We were fortunate to have a single research clinician evaluate each participant. Although approximately half of our study participants were referred to the study by another provider in the clinic who may have completed some of the routine clinical interview or work-up, pathogen detection was not associated with provider referral. It is, however, important to note that our study population consisted of men who enrolled in a treatment

trial for NGU, and these men may not be representative of NGU patients in general. Lastly, given the extent of our exploratory analysis and the large number of comparative analyses performed, we acknowledge that some of our findings may be due to chance alone. Subsequent hypothesis-driven analyses would be better suited to inform definitive clinical practice decisions.

In conclusion, NGU is a heterogeneous condition associated with a variety of demographic, behavioral, and clinical features, some of which were pathogen specific. Pathogen detection among NGU cases in our study was associated with a variety of traditional STI risk factors and clinical features, whereas men with idiopathic urethritis were characterized by factors common in men typically considered to be at lower risk. Our findings may help to presumptively identify the etiology of NGU in the absence of pathogen-specific test results.

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TABLE 1

Sociodemographic, Behavioral, and Clinical Characteristics of 367 Men Enrolled in a Treatment Trial for Nongonococcal Urethritis (NGU), Stratified by Etiology

Characteristic [†]	CT+ (n = 82)	MG+ (n = 46)	TV+ (n = 9)	UU+ (n = 88)	Idiopathic CT/MG/TV/UU – (n = 168)
Sociodemographic characteristics					
Age (yr)	31.2(±9.0) [§]	30.3 (±7.4) [§]	41.8 (±5.3) [‡]	32.9 (±9.6)	35.5 (±9.9) [§]
Black race	30 (38.0%)	23 (53.5%) [‡]	9 (100%) [¶]	47 (54.7%) [¶]	49 (29.7%) [¶]
No education beyond high school	34 (42.5%)	21 (45.7%)	7 (77.8%) [‡]	51 (58.0%) [¶]	56 (33.3%) [§]
Annual income <\$ 10,000	23 (29.5%)	20 (45.5%)	6 (66.7%)	45 (52.3%) [¶]	49 (29.5%) [‡]
Behavioral characteristics					
Ever spent a night in jail	30 (37.0%)	26 (56.5%)	8 (88.9%) [§]	44 (50.6%) [‡]	63 (37.5%)
Crack cocaine use	7 (8.6%) [‡]	12 (26.1%)	2 (22.2%)	18 (20.7%)	26 (15.5%)
Received money for sex	5 (6.3%)	7 (15.2%) [‡]	0 (0.0%)	3 (3.4%)	9 (5.6%)
No. sex partners, past 2 mo	2 (1–3)	2 (1–2.5)	2 (2–2)	2 (1–3)	1 (1–2) ^{‡***}
Any female sex partners, past 2 mo	51 (63.0%)	30 (66.7%)	9 (100.0%)	70 (83.3%) [¶]	114 (67.9%)
Any male sex partners, past 2 mo	33 (40.2%) [¶]	13 (28.9%)	0 (0.0%)	13 (14.9%) [§]	39 (23.8%)
Characteristics of the most recent sex partner within 2 mo ^{††‡‡}					
Age of partner (yr)	28.9 (±9.0)	29.8 (±7.2)	37.0 (±8.4) [‡]	29.7 (±9.3)	30.0 (±9.2)
Age difference (yr)	–2.5 (±9.1)	–1.1 (±5.5)	–4.9 (±8.0)	–3.7 (±8.0)	–4.3 (±9.0)
Male partner	32 (50.0%) [¶]	13 (31.7%)	0 (0.0%)	14 (18.9%) [§]	37 (28.2%)
Black partner	14 (23.7%)	16 (43.2%) [§]	3 (42.9%)	20 (28.2%)	27 (22.5%)
Insertive anal sex with partner	25 (39.1%) [§]	14 (34.2%)	2 (25.0%)	15 (20.6%)	28 (21.4%)
Partnership duration (d)	16 (1–285)	75 (4–585)	374.5 (145–629) ^{‡***}	32 (1–363)	32 (1–503)
Complaints					
Urethral discharge	39 (47.6%)	30 (65.2%) [‡]	7 (77.8%)	50 (56.8%)	75 (44.6%) [‡]
Duration prior to clinic visit (d) ^{§§}	7 (3–12.5) ^{‡***}	5 (3–7)	4 (3–7)	5 (2–7)	3 (2–7) ^{§**}
Dysuria	47 (57.3%)	29 (63.0%)	3 (33.3%)	44 (50.0%)	72 (42.9%) [‡]
Duration prior to clinic visit (d) ^{††‡‡§§}	7 (4–14) ^{§**}	6 (3–10)	17.5 (5–30)	7 (2–10)	3 (2–7) ^{‡**}
Itching in penis ^{¶¶}	38 (48.1%)	25 (54.4%)	4 (50.0%)	39 (45.4%)	57 (34.3%) [§]
Medical history					
History of NGU	13 (16.5%) [§]	16 (35.6%)	4 (57.1%)	20 (23.8%)	60 (38.2%) [§]
History of depression diagnosis ^{††}	7 (15.9%)	5 (17.2%)	0 (0.0%)	8 (17.8%)	32 (33.7%) [§]
Examination					
Voided within 2 h of examination	21 (25.9%) [‡]	7 (15.2%)	1 (12.5%)	13 (14.9%)	23 (15.5%)

Characteristic [†]	CT+ (n = 82)	MG+ (n = 46)	TV+ (n = 9)	UU+ (n = 88)	Idiopathic CT/MG/TV/UU – (n = 168)
Moderate or large amount of discharge present	32 (40.5%)	17 (37.8%)	4 (44.4%)	35 (40.2%)	50 (29.8%)
Cloudy or purulent discharge present ^{***}	39 (51.3%)	27 (61.4%)[‡]	7 (77.8%)	54 (62.8%)[§]	54 (38.0%)[§]
5 PMNs/HPF	81 (98.8%)[¶]	44 (95.7%)	9 (100.0%)	80 (90.9%)	126 (85.1%)[‡]
10 PMNs/HPF	60 (73.2%)[§]	31 (67.4%)	8 (88.9%)	61 (69.3%)	80 (54.1%)[‡]
Discharge present and <5 PMNs/HPF	1 (1.2%)[¶]	2 (4.4%)	0 (0.0%)	8 (9.1%)	22 (14.9%)[‡]
Discharge absent and 5 PMNs/HPF	5 (6.1%)	2 (4.4%)	1 (11.1%)	7 (8.0%)	20 (13.5%)
Discharge present and 5 PMNs/HPF	76 (92.7%)[¶]	42 (91.3%)[‡]	8 (88.9%)	73 (83.0%)	106 (71.6%)[§]
Co-infections					
CT+	—	8 (17.4%)	0 (0.0%)	13 (14.9%)	—
MG+	8 (10.1%)	—	0 (0.0%)	16 (18.4%)	—
TV+	0 (0.0%)	0 (0.0%)	—	5 (5.8%)[‡]	—
UU+	13 (16.5%)	16 (34.8%)	5 (62.5%)[‡]	—	—
UP+	10 (12.7%)	4 (8.7%)	2 (25.0%)	6 (6.9%)[‡]	—
Any pathogen(s) detected (CT/MG/TV/UU)	17 (21.5%)[§]	20 (43.5%)	5 (62.5%)	30 (34.5%)	—
Any organism(s) detected (CT/MG/TV/UU/UP)	24 (30.4%)[§]	23 (50.0%)	7 (87.5%)	33 (37.9%)	—

N (%) displayed for categorical variables, among participants with non-missing data. Mean (±SD) computed for normally distributed variables.

Median (interquartile range) computed for non-normally distributed variables.

Boldface type indicates a statistically significant 2-sample *t* test, χ^2 test, Wilcoxon rank sum test (**), or Fisher exact test (||) for comparison of cases to specified referent group with the following symbols denoting the level of significance:

In each column, men with the designated pathogen detected were compared to men without the pathogen. The idiopathic cases are compared to cases with any pathogen detected. Column categories are not mutually exclusive. Thirty-five men had more than 1 pathogen detected and are represented in each applicable column. Thirteen CT/MG/TV-negative cases who lacked speciated ureaplasma results are not explicitly represented in any of the column categories because their undetermined UU infection status precluded their inclusion in the UU-positive and idiopathic categories. These men were included in the referent groups for analyses of CT, MG, and TV infection.

CT-positive (n = 64), MG-positive (n = 41), TV-positive (n = 8), UU-positive (n = 74), and idiopathic (n = 131) cases. These data were not available for 19.6% of participants because they were not asked (n = 9), chose not to provide this information (n = 2), reported no sex in the previous 2 months (n = 14), or the data they did provide was not analyzed because the dates of the sexual encounters reported by the study participants did not fall within the 2 months prior to the interview (n = 47). When multiple partnerships were reported, data from the most recent partnership were summarized.

CT indicates *Chlamydia trachomatis*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; UU, *Ureaplasma urealyticum*; NGU, nongonococcal urethritis; 5 PMNs/HPF, 5 polymorphonuclear leukocytes per high-powered field (1000X) averaged over 3 fields on a urethral Gram-stain.

[‡]*P* 0.05

[§]*P* 0.01, and

[¶]*P* 0.001.

[†]Other characteristics that were evaluated but were not significantly associated with CT, MG, TV, UU, UP, or idiopathic urethritis were Hispanic ethnicity; birthplace outside of the United States; ever using injection drugs, methamphetamine/crystal, or ecstasy; ever using Viagra, Cialis, or Levitra; ever paying money for sex; ever having sex with an injection drug user; ever having sex with a transgendered partner; ever meeting a partner through the internet; always using condoms for vaginal sex; always using condoms for insertive anal sex; having any new sex partners in

the past 2 months (and number of new partners); complaints of “other” urethral symptoms (and duration) or genital lesions (and duration); self-reported history of gonorrhea, chlamydia, genital warts, or genital herpes; time since last antibiotic use; circumcision status; urethral discharge (presence or amount); genital lesion or rash; abnormal scrotal contents or inguinal lymph nodes; partner ethnicity; type of partnership (“main” vs. “casual”); frequency of condom use with partner; vaginal sex with partner (if female); giving/receiving oral sex with partner; and knowing or suspecting that their partner had concurrent partners (if they had sex on 1 occasion).

†† Variable with >10% missing data.

‡‡ Among men who provided detailed partner-specific information on the CASI regarding sex partners from the 60 days prior to enrollment;

§§ Among study participants with the specified symptom.

¶¶ Itching symptom data were explicitly captured on the CASI questionnaire. All other symptom data were captured on a standardized clinic chart during the clinician interview.

//// Versus no discharge or small amount of discharge.

*** Versus no discharge or clear discharge.

TABLE 2

Factors Independently Associated With Detection of CT, MG, UU, and Idiopathic Urethritis Among Men With NGU

Covariate	Adjusted Relative Risk (95% CI)			
	CT	MG	UU	Idiopathic CT/MG/TV/UU-
Sociodemographic characteristics				
Age (per year increase)	0.97 (0.95–0.99) *	0.94 (0.91–0.97) †	0.99 (0.97–1.01)	1.02 (1.01–1.03) †
Black race	1.5 (0.99–2.3)	2.0 (1.2–3.4) *	1.2 (0.8–1.8)	0.7 (0.5–0.9) ‡
No education beyond high school	—	—	1.7 (1.1–2.6) *	—
Behavioral characteristics				
Received money for sex	—	3.7 (1.9–7.3) †	—	—
Any female sex partners, past 2 mo	—	—	2.0 (1.1–3.7) *	—
Any male sex partners, past 2 mo	2.0 (1.3–3.0) †	—	—	—
Complaints				
Urethral discharge	—	1.8 (1.01–3.1) *	—	—
Itching in penis	—	—	—	0.7 (0.6–0.9) ‡
Medical history				
History of NGU	0.5 (0.3–0.9) *	—	—	1.4 (1.1–1.7) ‡
Examination				
Cloudy or purulent discharge present	—	—	1.6 (1.1–2.5) *	0.7 (0.5–0.95) *
Discharge present and ≥ 5 PMNs/HPF	3.4 (1.5–8.0) ‡	—	—	0.8 (0.6–0.96) *
Coinfections				
Any other pathogen(s) detected (CT/MG/TV/UU)	0.5 (0.3–0.8) ‡	0.9 (0.5–1.5)	0.8 (0.5–1.2)	NA

Adjusted relative risks and 95% confidence intervals (95% CI) are displayed for covariates included in each pathogen-specific multivariable model. Models were fit using a manual backward step wise approach. All models adjusted for age, race, and coinfection with any other pathogens. Boldface type indicates a statistically significant independent association with the following symbols denoting the level of significance:

CT indicates *Chlamydia trachomatis*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; UU, *Ureaplasma urealyticum*; NGU, nongonococcal urethritis; ≥ 5 PMNs/HPF, ≥ 5 polymorphonuclear leukocytes per high-powered field (1000X) averaged over ≥ 3 fields on a urethral Gram-stain; NA, not applicable.

* $P \leq 0.05$,

† $P \leq 0.01$, and

‡ $P \leq 0.001$.