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Cross-sectional study of urethral exposures at last sexual episode associated with non-gonococcal urethritis among STD clinic patients

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Abstract

Objective—Although *Chlamydia trachomatis* (CT) and *Mycoplasma genitalium* (MG) are major causes of non-gonococcal urethritis (NGU), up to 50% of cases are of unknown aetiology. We sought to identify urethral exposures at last sexual episode associated with NGU and non-CT/non-MG NGU to identify anatomical sites from which aetiologically relevant micro-organisms may be acquired.

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Competing interests CMK and LEM have received donations of test kits and reagents from Hologic. All other authors declare that they have no conflict of interest.

Patient consent All patients provided written, informed consent for this study.

Ethics approval This study was approved by the University of Washington Human Subjects Division, IRB Committee J (STUDY00002016).

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Data sharing statement This study is nested within a larger project. Data will be made available to other investigators after the completion of the project and publication of additional key results.

Methods—We enrolled STD clinic patients with and without NGU assigned male sex at birth and age 16 into a cross-sectional study. NGU was urethral symptoms or visible discharge plus 5 polymorphonuclear leucocytes without *Neisseria gonorrhoeae*. Urine was tested for CT and MG (Aptima). We used logistic regression to estimate the association between urethral exposures at last sex and NGU separately among cisgender men and transgender women who have sex with men (MSM/TGWSM) and cisgender men who have sex with women (MSW).

Results—Between 8 August 2014 and 1 November 2017, we enrolled 432 patients, including 183 MSM/TGWSM (118 NGU+, 65 NGU−) and 249 MSW (126 NGU+, 123 NGU−). The mean age was 34; 59% were white. CT and MG were detected in 72 (30%) and 49 (20%) NGU+ participants, respectively. Compared with MSM/TGWSM reporting only non-urethral exposures at last sex, those reporting insertive anal intercourse (IAI) only (adjusted OR (AOR)=4.46, 95% CI 1.09 to 18.19) and IAI with insertive oral sex (IOS) (AOR=7.88, 95% CI 2.67 to 23.26) had higher odds of NGU. MSM/TGWSM reporting IOS only had no significant increased odds (AOR=1.67, 95% CI 0.58 to 4.85). Compared with MSW whose only urethral exposure at last sex was vaginal sex (VS), MSW reporting IOS and VS had similar odds of NGU (OR=0.84, 95% CI 0.50 to 1.41). The results were similar for non-CT/non-MG NGU.

Conclusions—Among MSM/TGWSM, IAI may lead to transmission of yet-unidentified rectal micro-organisms that cause non-CT/non-MG NGU, in addition to transmission of known pathogens. Sites of urethral exposure appear less important for understanding NGU risk among MSW due to minimal variation in behaviour.

INTRODUCTION

Non-gonococcal urethritis (NGU) is the most common male genital tract syndrome and leads to >200 000 physician visits per year in the USA.¹ NGU is characterised by urethral symptoms and elevated polymorphonuclear leucocytes (PMNs) in the absence of *Neisseria gonorrhoeae* (NG) and has infectious and potentially non-infectious causes.² Although the sequelae associated with NGU are rare, the pathogens that cause NGU are sexually transmitted and carry a high risk of sequelae in women (eg, pelvic inflammatory disease, ectopic pregnancy, infertility).³ Moreover, the inflammation associated with NGU may increase risk of HIV acquisition and transmission.^{4,5} Thus, prevention and appropriate clinical management of NGU are critical for reproductive health and HIV prevention.

However, prevention and management of NGU are challenging. Although *Chlamydia trachomatis* (CT) and *Mycoplasma genitalium* (MG) are major causes of NGU, up to 50% of cases are of other or unknown aetiology. Clinical testing for MG and less common causes (eg, *Trichomonas vaginalis*, adenovirus, herpes simplex virus) is uncommon in many settings.² Thus, presumptive therapy active against CT is generally provided to patients with NGU,⁶ with treatment failure rates of up to 20%.⁷ An improved understanding of the aetiologies of non-CT/non-MG NGU would inform targeted NGU diagnosis, treatment and prevention.

Some evidence suggests that the aetiology of NGU may differ for men who have sex with men (MSM) and men who have sex with women (MSW). MSM with NGU have more often reported urethral discharge and dysuria,⁷ more often tested negative for known pathogens,^{7–9}

and had a different distribution of NGU-associated pathogens than MSW⁷⁹ Different aetiological agents of NGU in MSM and MSW could result from urethral exposure to different anatomical sites during sex or different bacteria within the same anatomical site of men versus women. However, the sexual behaviours associated with NGU have been evaluated primarily in separate studies of MSM¹⁰¹¹ and MSW.^{12–14} One study included MSM and MSW but did not evaluate the behaviours associated with NGU separately by sex of sex partners.¹⁵ Moreover, published studies to date have evaluated the role of behaviours in the past 1¹²¹⁵ or 2¹⁰¹¹¹³¹⁴ months. Empirical analyses of comparable data in both populations that examine behaviours during aetiologically relevant time frames may identify anatomical sites from which known and unknown micro-organisms are acquired.

To address these knowledge gaps, we evaluated urethral exposures at last sexual episode associated with NGU and non-CT/non-MG NGU among MSM and MSW. We hypothesised that insertive anal intercourse (IAI) at last sex would be associated with NGU among MSM and MSW, but that insertive oral sex (IOS) at last sex would be associated with NGU only among MSM, consistent with prior observations.^{10–14}

MATERIALS AND METHODS

Study design and procedures

We recruited persons assigned male sex at birth and age ≥ 16 years attending the Public Health – Seattle & King County (PHSKC) STD Clinic into this cross-sectional study. Individuals who self-identified as cisgender men, transgender women or non-binary were eligible. We required participants to have had exclusively male or exclusively female sex partners in the past year. Patients who had both male and female partners in the past year, no sex in the past 60 days, antibiotics in the past 30 days, known urethral contact to NG, or urethral NG diagnosed by Gram stain or nucleic acid amplification testing were not eligible. The participants included in this analysis were enrolled into either a cross-sectional (42%) or cohort (58%) study. We included only the enrolment visit data for cohort participants.

All clinic patients complete a clinical computer-assisted self-interview (CASI) providing sociobehavioural and clinical information. Potentially eligible patients saw one of two study clinicians who confirmed eligibility and offered enrolment. Patients were offered \$25 for participation. They underwent standard clinical interview and genital examination, including collection of 30–45 mL of first-void urine and a urethral swab specimen for Gram staining. The Gram-stained slide of urethral exudates was examined to quantitate PMNs and identify Gram-negative intracellular diplococci indicative of urethral NG. We defined NGU as urethral symptoms (urethral discharge, dysuria or other urethral symptoms) or visible urethral discharge on examination, in combination with ≥ 5 PMNs per high power field (HPF) assessed over the three most populated oil immersion fields. Our comparison group of patients without NGU was defined as those without urethral symptoms, without visible urethral discharge and with <5 PMNs/HPF. Patients who did not meet our study NGU definition but had either (1) urethral symptoms or visible discharge or (2) ≥ 5 PMNs/HPF alone, but not both, were excluded from this analysis. The urine specimen was tested for NG and CT using the Aptima Combo 2 Assay and MG using the Aptima Assay with analyte-specific reagents (Hologic, San Diego, California). Participants also completed a study CASI

developed with Research Electronic Data Capture (REDCap)¹⁶ to collect additional sociobehavioural data, including recent sexual exposures and condom use.

Statistical analysis

We compared the characteristics of patients with and without NGU using Fisher's exact tests and two-sample t-tests with unequal variances. To identify urethral exposures at last sex associated with NGU, we fit two separate multivariable logistic regression models with robust SEs: one for MSM and transgender women who have sex with men (TGWSM) and one for MSW. Due to very different distributions of urethral exposures at last sex, exposure variables for MSM/TGWSM and MSW were categorised differently. For MSM/TGWSM, we created four mutually exclusive categories of urethral exposures: (1) non-urethral exposures only (receptive oral sex, receptive anal sex, rimming, hand-penile contact), (2) IOS only, (3) IAI only, and (4) IOS and IAI. For MSW, we created two mutually exclusive categories of urethral exposures: (1) vaginal sex (VS) only and (2) IOS and VS only. MSW reporting other combinations of behaviours (n=21, 8%) were excluded from this analysis.

Initially, for MSM/TGWSM and MSW, we included the respective exposure variable as dummy variables, condom use with last sex partner (always/not always) and our hypothesised confounders (age (continuous), known HIV-positive status (MSM/TGWSM only), HIV pre-exposure prophylaxis (PrEP) use (MSM/TGWSM only) and number of sex partners with whom participants engaged in each behaviour (IOS, IAI and VS (MSW only)) in the past 2 months). Covariates were only retained in a final model if they changed an exposure effect estimate by >10%. We also evaluated interaction terms for each exposure and condom use with last sex partner; however, there was no evidence that condom use modified the relationship between any urethral exposure and NGU for MSM/TGWSM or MSW ($p>0.35$), so no interaction terms were included in the final models.

In a secondary analysis of non-CT/non-MG NGU, we restricted the study sample to participants with negative tests for both CT and MG. The same analysis described above was performed.

All participants provided written, informed consent. We used Stata V13 for analyses, two-sided tests and significance level $\alpha=0.05$.

RESULTS

Between 8 August 2014 and 1 November 2017, we approached 1719 patients attending the PHSKC STD Clinic about this study, of whom 332 (19%) were ineligible and 874 (51%) declined participation. The main reasons for declining were inability to attend cohort study follow-up visits (43%) and preference not to collect urethral swabs (22%). Those who declined were similar to those who enrolled with respect to race but less often reported Hispanic/Latino ethnicity ($p<0.01$) and more often were screened for the cohort study only ($p<0.01$). Of the 513 patients who enrolled, a further 81 (16%) were excluded from this analysis because they did not meet the study NGU definition. The remaining 432 patients constituted this study sample, including 183 MSM and 2 TGWSM (analysed together due to

the small number of TGWSM, 118 with and 65 without NGU) and 249 MSW (126 with and 123 without NGU).

Among all participants, the mean age was 34 years (SD = 9.9, range = 19–71), most reported white (59%) or black (18%) race, and 14% reported Hispanic/Latino ethnicity. Most participants with NGU were attending the clinic for evaluation of urethral symptoms (77%), while most participants without NGU sought STD testing (78%) (table 1).

Compared with participants without NGU, those with NGU were more likely to be black ($p = 0.02$); participants with non-CT/non-MG NGU reported a lower income level ($p = 0.04$). History of NGU, NG and CT were each associated with any NGU and non-CT/non-MG NGU ($p < 0.01$). CT and MG were detected in 72 (30%) and 49 (20%) participants with NGU, respectively. Sociodemographic and clinical characteristics associated with NGU were similar for MSM/TGWSM and MSW with a few exceptions. Among MSM/TGWSM but not MSW, higher education level was associated with any NGU ($p = 0.01$). Among MSW but not MSM/TGWSM, black race ($p < 0.01$) and lower income level ($p = 0.04$) were associated with any NGU.

Participants' clinical presentation of NGU was similar, irrespective of whether CT or MG was detected (table 2). Of 244 participants with any NGU, 218 (89%) reported urethral symptoms. Dysuria was the most common symptom (64%). On examination, 218 (89%) participants with any NGU had a visible urethral discharge, which was most often clear (59%); most (77%) had 10PMNs/HPF. The clinical presentation of MSM/TGWSM and MSW with NGU was similar with one exception. Among participants with visible discharge, MSM/TGWSM were somewhat more likely to have clear discharge than MSW (66% vs 53%, $p = 0.054$).

Sexual behaviour

Among MSM/TGWSM, 49 (27%) reported IOS as their only urethral exposure at last sexual episode, 24 (13%) reported IAI only, and 84 (47%) reported both IOS and IAI (table 3). The remaining 23 (13%) MSM/TGWSM reported only non-urethral exposures at last sex. In bivariate analyses, IAI only and IAI with IOS were more commonly reported at last sex among MSM/TGWSM with than without NGU ($p < 0.01$). The sexual behaviours associated with non-CT/non-MG NGU among MSM/TGWSM were similar to those observed for any NGU (data not shown).

Nearly all MSW (95%) reported VS at last sex, irrespective of NGU status. More specifically, 10 (4%) MSW reported IOS alone, 110 (45%) reported VS alone, 120 (49%) reported IOS and VS, 2 (1%) reported IAI and VS, and 4 (2%) reported all three behaviours (IOS, IAI and VS). No MSW reported only non-urethral exposures at last sex. In bivariate analyses, none of the urethral exposures at last sex were more common among MSW with than without NGU ($p = 0.8$). MSW with NGU reported more partners in their lifetime ($p = 0.01$) but a similar number of partners in the past 2 months compared with MSW without NGU. However, MSW with NGU less often reported always using condoms with their last partner (15% vs 27%, $p = 0.03$). No sexual behaviours were associated with non-CT/non-MG NGU among MSW (data not shown).

Multivariable analyses: any NGU

Compared with MSM/TGWSM reporting only non-urethral exposures at last sexual episode, MSM/TGWSM whose urethral exposures were IAI only and IAI with IOS had significantly higher odds of NGU, adjusting for condom use with last partner and number of IOS and number of IAI partners in the past 2 months (adjusted OR (AOR)=4.46 (95% CI 1.09 to 18.19) and AOR=7.88 (95% CI 2.67 to 23.26), respectively) (table 4). MSM/TGWSM whose only urethral exposure was IOS had no significantly increased odds (AOR=1.67, 95% CI 0.58 to 4.85). Further adjustment for age, known HIV-positive status and PrEP use did not appreciably change these estimates.

Among MSW, those whose only urethral exposure at last sex was VS had similar odds of NGU as those reporting IOS and VS only (OR=0.84, 95% CI 0.50 to 1.41). Adjusting for age, condom use with last partner, and number of IOS, IAI or VS partners in the past 2 months did not meaningfully change these estimates.

Multivariable analyses: non-CT, non-MG NGU

The results were similar when we restricted the analysis to patients without CT and MG. Compared with MSM/TGWSM reporting only non-urethral exposures at last sex, those whose urethral exposures were IOS only, IAI only, and IOS and IAI had 2.03 (95% CI 0.58 to 7.18), 3.54 (95% CI 0.81 to 15.55) and 6.85 (95% CI 1.87 to 25.04) times the odds of non-CT/non-MG NGU, respectively, adjusting for the number of IOS and the number of IAI partners in the past 2 months. MSW whose urethral exposures at last sex were IOS and VS had similar odds of non-CT/non-MG NGU as those whose only urethral exposure was VS.

DISCUSSION

Among MSM and TGWSM attending an STD clinic in Seattle, Washington, IAI at last sex with or without IOS was strongly associated with any NGU and non-CT/non-MG NGU, while IOS alone was not associated with either outcome. The sociodemographic characteristics and urethral sexual exposures associated with NGU differed somewhat for MSM/TGWSM and MSW although the clinical presentation of NGU was similar. Among MSW, there was minimal variation in urethral exposures at last sex, and no evidence that IOS in combination with VS was associated with higher odds of NGU or non-CT/non-MG NGU than VS alone.

We hypothesised that IOS at last sex would be associated with NGU among MSM and TGWSM but not MSW based on four prior studies in Seattle. Two studies of MSM found that IOS in the past 2 months was associated with non-CT NGU,^{10,11} while two studies of MSW found that IOS in the past 2 months was not associated with NGU¹⁴ or pathogen-negative NGU.¹³ In contrast, we did not observe any association between IOS at last sex and either NGU or non-CT/non-MG NGU, and this was true for MSM/TGWSM and MSW. Differences in the timing of sexual exposures, NGU definitions, comparison groups or methodology across studies may explain the inconsistent results.

Our study suggests that IAI at last sex is associated with both NGU overall and non-CT/non-MG NGU among MSM and TGWSM. This reinforces that transmission of CT and MG can

occur via IAI and suggests that rectal micro-organisms may be important in the aetiology of non-CT/non-MG NGU. Prior studies of IAI and NGU have yielded inconsistent results. Two studies of MSM suggested that IAI in the past 2 months was independently associated with urethral CT but reported conflicting results for whether IAI was associated with non-CT NGU.^{10,11} In contrast, a study of Australian MSM and MSW found that condomless IAI in the past month was consistently *less* common among men with NGU, although they did not evaluate MSM and MSW separately.¹⁵ In our study, IAI with and without IOS at the most recent sexual episode was associated with over fourfold increased odds of NGU among MSM and TGWSM. The disparate results across studies may be due to variation in the epidemiology of NGU-associated pathogens across settings, definition of NGU across studies, time frame of sexual exposures considered or study methodology. Future studies of the composition of the urethral microbiota of MSM and TGWSM with and without NGU would help determine whether known rectal bacteria cause non-CT/non-MG NGU in some cases.

Our finding that MSW had minimal variation in urethral exposures at last sex and similar odds of NGU after VS alone or in combination with IOS suggests that specific anatomical sites of urethral exposure are not key for understanding NGU risk among MSW. Instead, population-level factors associated with prevalence of pathogens or polymicrobial communities among sex partners may be more relevant for NGU risk among MSW. For example, among MSW in Seattle, *Leptotrichia/Sneathia* species were associated with NGU and detected in 15% of men with pathogen-negative NGU.¹³ These bacteria are prevalent in women with bacterial vaginosis (BV)^{17,18} and may have been acquired from or shared with female partners with BV during VS. Future studies of partner characteristics and urethral microbiota associated with non-CT/non-MG NGU among MSW may help define risk factors for these NGU cases.

Our analysis was strengthened by the requirement of objective evidence of urethritis (≥ 5 PMNs/HPF), use of CASI to minimise social desirability bias in our sexual behaviour data,^{19–21} and consideration of urethral exposures at last sex which may be most aetiologically relevant. However, there were also limitations. First, while we collected data on condom use with participants' last partner, we did not obtain condom use separately for each urethral exposure. People may use a condom for some behaviours but not others within a sexual episode.²² Second, the last sexual episode may not be the aetiologically relevant exposure for some individuals, depending on how quickly they develop symptoms and seek care and how often they have sex. Third, IAI at last sex may be a marker of more frequent IAI, and cumulative exposure to rectal bacteria may be more important for NGU risk than the exposure to rectal bacteria at last sexual episode. We were not able to evaluate the frequency of IAI, although a proxy measure of this (number of different IAI partners) did not influence the relationship between IAI at last sex and NGU among MSM and TGWSM. Fourth, due to the small number of MSW who reported recent IAI (n=6), we could not estimate the association between IAI and NGU among MSW. Fifth, we did not test participants for some known causes of NGU that are uncommon in our population. Nonetheless, these pathogens may have caused some cases of non-CT/non-MG NGU. Sixth, our secondary analysis evaluating the relationship between urethral sexual exposures and non-CT/non-MG NGU had limited power; larger studies would be useful to confirm our findings. Seventh, a large

percentage of the patients approached about our study declined participation, many due to inability to attend parent cohort study follow-up. This may have biased our estimates if their sexual behaviour and NGU aetiology differ from that of the participants. Finally, our study only included two TGWSM, so our findings among MSM/TGWSM are most generalisable to MSM.

In conclusion, IAI appears to play a key role in the aetiology of non-CT/non-MG NGU among MSM and TGWSM, in addition to transmission of CT and MG. In contrast, anatomical sites of urethral sexual exposure among MSW do not appear to be important for understanding risk of non-CT/non-MG NGU, likely due to minimal variation in behaviour. Additional studies of the urethral microbiota, its determinants and the role of rectal bacteria are needed to fully describe the aetiologies of NGU and inform clinical management and prevention.

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REFERENCES

1. US Centers for disease control and prevention. Sexually transmitted disease surveillance 2000. Atlanta, GA, 2001.
2. Martin DH. DH Urethritis in males In: Holmes KK, Sparling PF, Stamm WE, Sexually transmitted diseases. 4th edn New York: McGraw Hill, 2008:1107–26.
3. Holmes KK, Stamm WE, Sobel JD. Lower genital tract infection syndromes in women In: Holmes KK, Sparling PF, Stamm WE, Sexually Transmitted Diseases. 4th ed. New York City: McGraw Hill, 2008:987–1016.
4. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. Lancet 1997;349:1868–73. [PubMed: 9217758]
5. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999;75:3–17. [PubMed: 10448335]
6. US Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. Atlanta, GA, 2015.
7. Manhart LE, Gillespie CW, Lowens MS, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial. Clin Infect Dis 2013;56:934–42. [PubMed: 23223595]
8. Rane VS, Fairley CK, Weerakoon A, et al. Characteristics of acute nongonococcal urethritis in men differ by sexual preference. J Clin Microbiol 2014;52:2971–6. [PubMed: 24899041]
9. Bradshaw CS, Tabrizi SN, Read TR, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. J Infect Dis 2006;193:336–45. [PubMed: 16388480]
10. Lafferty WE, Hughes JP, Handsfield HH. Sexually transmitted diseases in men who have sex with men. Acquisition of gonorrhea and nongonococcal urethritis by fellatio and implications for STD/HIV prevention. Sex Transm Dis 1997;24:272–8. [PubMed: 9153736]

11. Barbee LA, Khosropour CM, Dombrowski JC, et al. An estimate of the proportion of symptomatic gonococcal, chlamydial and non-gonococcal non-chlamydial urethritis attributable to oral sex among men who have sex with men: a case-control study. *Sex Transm Infect* 2016;92:155–60. [PubMed: 26297719]
12. Iser P, Read TH, Tabrizi S, et al. Symptoms of non-gonococcal urethritis in heterosexual men: a case control study. *Sex Transm Infect* 2005;81:163–5. [PubMed: 15800097]
13. Manhart LE, Khosropour CM, Liu C, et al. Bacterial vaginosis-associated bacteria in men: association of *Leptotrichia/Sneathia* spp. with nongonococcal urethritis. *Sex Transm Dis* 2013;40:944–9. [PubMed: 24220356]
14. Schwartz MA, Lafferty WE, Hughes JP, et al. Risk factors for urethritis in heterosexual men. The role of fellatio and other sexual practices. *Sex Transm Dis* 1997;24:449–55. [PubMed: 9293607]
15. Couldwell DL, Gidding HF, Freedman EV, et al. *Ureaplasma urealyticum* is significantly associated with non-gonococcal urethritis in heterosexual Sydney men. *Int J STD AIDS* 2010;21:337–41. [PubMed: 20498103]
16. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J BiomedInform* 2009;42:377–81.
17. Haggerty CL, Totten PA, Ferris M, et al. Clinical characteristics of bacterial vaginosis among women testing positive for fastidious bacteria. *Sex Transm Infect* 2009;85:242–8. [PubMed: 19004865]
18. Srinivasan S, Hoffman NG, Morgan MT, et al. Bacterial communities in women with bacterial vaginosis: high resolution phylogenetic analyses reveal relationships of microbiota to clinical criteria. *PLoS One* 2012;7:e37818. [PubMed: 22719852]
19. Kurth AE, Martin DP, Golden MR, et al. A comparison between audio computer-assisted self-interviews and clinician interviews for obtaining the sexual history. *Sex Transm Dis* 2004;31:719–26. [PubMed: 15608586]
20. Rogers SM, Willis G, Al-Tayyib A, et al. Audio computer assisted interviewing to measure HIV risk behaviours in a clinic population. *Sex Transm Infect* 2005;81:501–7. [PubMed: 16326855]
21. Richens J, Copas A, Sadiq ST, et al. A randomised controlled trial of computer-assisted interviewing in sexual health clinics. *Sex Transm Infect* 2010;86:310–4. [PubMed: 20551234]
22. Tieu HV, Li X, Donnell D, et al. Anal sex role segregation and versatility among men who have sex with men: EXPLORE Study. *J Acquir Immune Defic Syndr* 2013;64:121–5.

Key messages

- Recent insertive anal intercourse was strongly associated with non-gonococcal urethritis (NGU) among men who have sex with men and transgender women who have sex with men, likely reflecting efficient transmission of *Chlamydia trachomatis* and *Mycoplasma genitalium*, as well as yet-unidentified rectal micro-organisms.
- Specific anatomical sites of urethral exposure do not appear to be key for understanding NGU risk among men who have sex with women due to minimal variation in sexual behaviour.

Table 1
 Characteristics of participants with and without NGU, overall and for non-CT/non-MG NGU

Characteristics [*]	No NGU (n=188) n (%)	Any NGU (n=244) n (%)	P values [†]	Non-CT/non-MG NGU [‡] (n=129) n (%)	P values [‡]
Sociobehavioural					
Gender and sex of sex partners					
MSM	64 (34)	117 (48)		56 (43)	
TGWSM	1 (1)	1 (<1)		1 (1)	
MSW	123 (25)	126 (52)	0.006	72 (56)	0.127
Age, mean±SD	34.3±10.4	33.8±9.6	0.596 [§]	35.4±10.3	0.383 [§]
Race					
White	123 (65)	130 (53)		72 (56)	
Black	24 (13)	53 (22)		30 (23)	
Other/Multiple/Unknown	41 (22)	61 (25)	0.019	27 (21)	0.064
Hispanic or Latino ethnicity					
Yes	28 (15)	33 (14)		21 (16)	
No	154 (82)	203 (83)		102 (79)	
Unknown	6 (3)	8 (3)	0.953	6 (5)	0.428
Education completed					
High school or GED	74 (40)	94 (39)		54 (42)	
Some college	31 (17)	61 (25)		31 (24)	
College graduate	81 (44)	87 (36)	0.074	43 (34)	0.086
Income					
<\$10 000	36 (19)	52 (21)		24 (19)	
\$10 000–49 999	72 (38)	96 (39)		60 (47)	
\$50 000	56 (30)	48 (20)		21 (16)	
Declined/Unknown	24 (13)	48 (20)	0.051	24 (19)	0.043
Clinical					
Reason for visit[¶]					
Urethral symptoms	–	187 (77)	–	92 (71)	–
Other symptoms	32 (17)	1 (<1)	<0.0005	1 (1)	<0.0005

Characteristics*	No NGU (n=188) n (%)	Any NGU (n=244) n (%)	Non-CT/non-MG NGU [‡] (n=129) n (%)	P values [†]
STD testing	146 (78)	169 (70)	92 (72)	0.287
History of STD				
History of NGU	13 (7)	52 (21)	29 (23)	<0.0005
History of gonococcal infection	40 (21)	93 (38)	45 (35)	0.006
History of CT infection	52 (28)	117 (48)	57 (45)	0.001
Known HIV-positive**	2 (1)	12 (5)	4 (3)	0.237
HIV pre-exposure prophylaxis use ^{** ††}	10 (5)	18 (8)	7 (6)	0.801
STD pathogen detected				
<i>Chlamydia trachomatis</i>	0 (0)	72 (30)	–	–
<i>Mycoplasma genitalium</i>	6 (3)	49 (20)	–	–

* n=4 missing education completed, n=1 missing reason for visit is STD testing, n=4 missing history of NGU, n=2 missing history of gonococcal infection and n=3 missing history of CT.

[†] Fisher's exact test unless otherwise specified. Bold indicates significance at alpha=0.05 level.

[‡] Urine specimen tested for CT and MG via Aptima Assay. Comparison group is participants without NGU whose urine samples tested negative for CT or MG (excludes n=6 participants with MG).

[§] Two-sample t-test with unequal variances.

[¶] Multiple reasons for visit possible. Other symptoms include genital lesions/rash, non-genital rash, anorectal symptoms, testicular symptoms, oral/pharyngeal symptoms and other symptoms.

^{**} All participants known to be living with HIV or taking HIV pre-exposure prophylaxis were MSM or TGWSM.

^{††} Among participants who were not known to be HIV-positive (n=186 no NGU, n=232 any NGU, n=125 non-CT/non-MG NGU).

CT, *Chlamydia trachomatis*; GED, General Education Diploma; MG, *Mycoplasma genitalium*; MSM, cisgender men who have sex with men only; MSW, cisgender men who have sex with women only; NGU, non-gonococcal urethritis; TGWSM, transgender women who have sex with men only.

Table 2

Clinical presentation of participants with NGU and non-CT/non-MG NGU

Characteristics	Any NGU (n=244) n (%)	Non-CT/non-MG NGU* (n=129) n (%)
Self-reported urethral symptoms	218 (89)	110 (85)
Type of urethral symptoms		
Urethral discharge	124 (57)	58 (53)
Dysuria	139 (64)	65 (59)
Other urethral symptoms [†]	112 (51)	61 (55)
Visible urethral discharge on examination	218 (89)	112 (87)
Characteristics of urethral discharge		
Clear	129 (59)	66 (59)
Cloudy	77 (35)	40 (36)
Purulent or mucoid	12 (6)	6 (5)
Amount of urethral discharge		
Small	147 (67)	72 (64)
Moderate	69 (32)	40 (36)
Large	2 (1)	0 (0)
Average PMNs/HPF on urethral Gram stain		
5–9 PMNs/HPF	55 (23)	35 (27)
10 PMNs/HPF	189 (77)	94 (73)

* Urine specimen tested for CT and MG via Aptima Assay.

[†] Includes urethral itching, tingling or other irritation.

CT, *Chlamydia trachomatis*; HPF, high power field; MG, *Mycoplasma genitalium*; NGU, non-gonococcal urethritis; PMN, polymorphonuclear leucocytes.

Table 3

Sexual behaviour of participants with and without NGU, stratified by sex of sex partners

Sexual behaviour [*]	MSM/TGWSM		MSW		P values [†]	NGU (n=126) n (%)	P values [‡]
	No NGU (n=65) n (%)	NGU (n=118) n (%)	No NGU (n=123) n (%)	NGU (n=126) n (%)			
Lifetime number of sex partners (any type of sex)							
1–4	3 (5)	3 (3)	5 (4)	1 (1)			
5–9	3 (5)	3 (3)	28 (23)	12 (10)			
10–24	8 (13)	16 (14)	32 (26)	42 (36)			
25	49 (78)	91 (81)	56 (46)	62 (53)	0.735		0.012
Number of sex partners in the past 2 months, mean±SD							
Any type of sex	5.0±7.1	4.7±5.8	2.0±2.2	2.3±2.3	0.798 [‡]		0.229 [‡]
Vaginal sex	–	–	2.2±3.1	2.3±2.3	–		0.794 [‡]
Insertive anal sex	2.2±5.1	3.4±4.2	0.3±0.7	0.2±0.5	0.125 [‡]		0.269 [‡]
Insertive oral sex	3.9±5.5	4.4±4.9	2.0±2.4	1.8±1.3	0.523 [‡]		0.537 [‡]
New sex partner in the past 2 months	45 (73)	96 (83)	79 (66)	90 (73)	0.117		0.265
Urethral exposures at last sexual episode [§]							
None (non-urethral exposures only)	14 (22)	9 (8)	0 (0)	0 (0)	<0.0005		0.783
Insertive oral sex only	25 (40)	24 (21)	4 (3)	6 (5)			
Insertive anal sex only	6 (10)	18 (15)	0 (0)	0 (0)			
Insertive oral sex and insertive anal sex only	18 (29)	66 (56)	0 (0)	0 (0)			
Vaginal sex only	–	–	51 (43)	59 (47)			
Insertive anal sex and vaginal sex only	–	–	1 (1)	1 (1)			
Insertive oral sex and vaginal sex only	–	–	61 (51)	59 (47)			
Insertive oral sex, insertive anal sex and vaginal sex	–	–	3 (3)	1 (1)			
Always used condoms with last sex partner	18 (29)	20 (18)	33 (27)	18 (15)	0.125		0.027

* n=18 missing lifetime number of sex partners, n=13 missing number of sex partners in the past 2 months, n=6 missing vaginal sex partners in the past 2 months, n=4 missing insertive anal sex partners in the past 2 months, n=8 missing insertive oral sex partners in the past 2 months, n=13 missing new sex partner in the past 2 months, n=4 missing behaviours at last sexual episode and n=14 missing condom use with the last sex partner.

[†]Fisher's exact test unless otherwise specified. Bold indicates significance at alpha=0.05 level.

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[‡]Two-sample t-test with unequal variances.
[§]Mutually exclusive categories.

MSM, cisgender men who have sex with men only; MSW, cisgender men who have sex with women only; NGU, non-gonococcal urethritis; TGWSM, transgender women who have sex with men only.

Multivariable analyses of associations of specific urethral exposures at last sexual episode with NGU and with non-CT/non-MG NGU, stratified by sex of sex partners

Table 4

Specific urethral exposures at last sexual episode	Any NGU		Non-CT/non-MG NGU [†]	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [‡]	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [§]
MSM/TGWSM [¶]				
Non-urethral exposures only	Ref	Ref	Ref	Ref
Insertive oral sex only	1.49 (0.54 to 4.10)	1.67 (0.58 to 4.85)	1.31 (0.41 to 4.48)	2.03 (0.58 to 7.18)
Insertive anal sex only	4.67 (1.34 to 16.30) [*]	4.46 (1.09 to 18.19) [*]	3.50 (0.85 to 14.39)	3.54 (0.81 to 15.55)
Insertive oral sex and insertive anal sex	5.70 (2.12 to 15.34) ^{**}	7.88 (2.67 to 23.26) ^{**}	4.20 (1.33 to 13.28) [*]	6.85 (1.87 to 25.04) ^{**}
MSW ^{††}				
Vaginal sex only	Ref	–	Ref	–
Vaginal sex and insertive oral sex only	0.84 (0.50 to 1.41)	–	0.98 (0.53 to 1.82)	–

^{*} P<0.05,

^{**} p<0.01.

[†] Analysis restricted to participants whose urine specimen tested negative for CT and MG via Aptima Assay.

[‡] For MSM/TGWSM, model adjusted for condom use with last partner (always/not always) and number of IAI and number of IOS partners in the past 2 months, additional adjustment for age (years), HIV status and PrEP use did not change these estimates by >10%. For MSW, adjusting for age, condom use with last partner, and number of IAI, IOS or VS partners in the past 2 months did not change these estimates by >10%.

[§] For MSM/TGWSM, model adjusted for number of IOS and number of IAI partners in the past 2 months, additional adjustment for age, HIV status, PrEP use and condom use with last partner did not change these estimates by >10%. For MSW, adjusting for age, condom use with last partner, and number of IOS, IAI or VS partners in the past 2 months did not change these estimates by >10%.

[¶] Per our study inclusion criteria, no MSM/TGWSM had VS in the past year.

^{††} Excludes n=21 MSW who reported other combinations of urethral exposures at last sexual episode (n=12 IOS only, n=3 IAI only, and n=6 IOS, IAI and VS). No MSW reported non-urethral exposures only at last sexual episode.

CT, *Chlamydia trachomatis*; IAI, insertive anal intercourse; IOS, insertive oral sex; MG, *Mycoplasma genitalium*; MSM, cisgender men who have sex with men only; MSW, cisgender men who have sex with women only; NGU, non-gonococcal urethritis; ref, reference; PrEP, pre-exposure prophylaxis; TGWSM, transgender women who have sex with men only; VS, vaginal sex.