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Characteristics of Acute Nongonococcal Urethritis in Men Differ by Sexual Preference

Vinita S. Rane,[b] Christopher K. Fairley,[a,b,c] Ajith Weerakoon,[d] Timothy H. Read,[a,b] Glenda Fehler,[b] Marcus Y. Chen,[a,b,c] Catriona S. Bradshaw[a,b,c]

Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia[a]; Melbourne Sexual Health Centre, Alfred Hospital, Carlton, Victoria, Australia[b]; Central Clinical School, Monash University, Clayton, Victoria, Australia[c]; Department of Health, Colombo, Central Province, Sri Lanka[d]

Nongonococcal urethritis (NGU) is a common clinical syndrome, but no etiological agent is identified in a significant proportion of cases. Whether the spectrum of pathogens differs between heterosexual men (MSW) and men who have sex with men (MSM) is largely unstudied but of considerable clinical relevance. A retrospective review was done using the electronic medical record database of Melbourne Sexual Health Centre, Australia. Cases were first presentations of symptomatic acute NGU with ≥5 polymorphonuclear leukocytes (PMNL)/high-powered field (HPF) on urethral Gram stain between January 2006 and December 2011. First-stream urine was tested for *Chlamydia trachomatis* and *Mycoplasma genitalium* by PCR. Demographic, laboratory, and behavioral characteristics of cases were examined by univariate and multivariable analyses. Of 1,295 first presentations of acute NGU, 401 (32%; 95% confidence interval [CI] of 29 to 34%) had *C. trachomatis* and 134 (11%; 95% CI of 9 to 13%) had *M. genitalium* detected. MSM with acute NGU were less likely to have *C. trachomatis* (adjusted odds ratio [AOR] = 0.4; 95% CI of 0.3 to 0.6) or *M. genitalium* (AOR = 0.5; 95% CI of 0.3 to 0.8) and more likely to have idiopathic NGU (AOR = 2.4; 95% CI of 1.8 to 3.3), to report 100% condom use for anal/vaginal sex (AOR = 3.6; 95% CI of 2.7 to 5.0), or to have engaged in sexual activities other than anal/vaginal sex (AOR = 8.0; 95% CI of 3.6 to 17.8). Even when *C. trachomatis* or *M. genitalium* was detected, MSM were more likely than MSW to report consistent condom use (OR = 4.7; 95% CI of 2.6 to 8.3). MSM with acute NGU are less likely to have the established bacterial sexually transmitted infections (STIs) and more likely to report protected anal sex or sexual activity other than anal sex prior to symptom onset than MSW. These data suggest that the etiologic spectrum of pathogens differs between MSM and MSW in acute NGU and that relatively low-risk practices are capable of inducing acute NGU.

Nucleic acid amplification techniques (NAAT) have allowed greater understanding of the variety of pathogens involved in acute nongonococcal urethritis (NGU) (1). This has included the recent recognition of *Mycoplasma genitalium*, herpes simplex virus (HSV), and adenoviruses as urethral pathogens (2–5), although in a significant proportion of cases no urethral pathogen is currently identified. The role of *Ureaplasma urealyticum* in NGU has been somewhat controversial, but recent evidence implicates specific biovars and possibly higher bacterial loads as causally associated with acute NGU (6–8). Sporadic case reports implicate other bacteria such as *Haemophilus* species (*Haemophilus influenzae* and *Haemophilus parainfluenzae*), *Streptococcus* species (*Streptococcus pneumoniae* and *Streptococcus pyogenes*), and *Moraxella catarrhalis* in acute NGU, following orogenital sex (9–11); however, their etiologic role has not been established in case-control studies.

Diagnostic and management approaches to acute NGU do not differentiate between men who have sex with men (MSM) and men who have sex with women (MSW). Yet sexual behaviors differ considerably between these groups, and it is therefore likely that the spectrum of pathogens varies. In support of this, a previous case-control study of NGU in our service found that *Chlamydia trachomatis* or *M. genitalium* were more likely to be associated with female partners, while viruses, such as HSV and adenovirus, were associated with a recent history of male sexual partners (2). Further elucidation of the etiology of this common syndrome, and developing an understanding of how sexual practices influence the detection of urethral pathogens, could improve the management of men and their partners (1, 12, 13). In this study, we examined behavioral, demographic, and laboratory characteristics of a large series of MSW and MSM with acute urethral symptoms over a 6-year period. We aimed to determine if there were key differences between MSW and MSM with acute NGU in the spectrum of pathogens involved and whether there were differences in sexual behavior preceding the acquisition of NGU.

MATERIALS AND METHODS

Study population. We retrospectively reviewed the electronic case record database of Melbourne Sexual Health Centre, the main public sexually transmitted diseases clinic in Melbourne, Australia, from January 2006 to December 2011. Patients were required to have the diagnosis of acute NGU entered into the electronic medical record, with one or more of the following acute urethral symptoms for less than 1 month's duration: urethral discharge and urethral irritation, discomfort, or itch; patients also needed to fulfill the conventional laboratory definition of urethritis, namely, 5 or more polymorphic neutrophilic lymphocytes/high-powered field (≥5 polymorphonuclear leukocytes [PMNL]/high-powered field [HPF]) on urethral Gram stain. Importantly, only a single first episode of acute NGU per case over the study period was included. All subsequent

Received 28 March 2014 Returned for modification 10 May 2014
Accepted 2 June 2014
Published ahead of print 4 June 2014
Editor: E. Munson
Address correspondence to Vinita S. Rane, vrane@mshc.org.au, or Catriona S. Bradshaw, cbradshaw@mshc.org.au.

doi:10.1128/JCM.00899-14

presentations with acute NGU during the study period were excluded. Clinical diagnoses and laboratory, demographic, and behavioral data for each consultation for acute NGU were recorded in a standardized format in the electronic medical record. From June 2008, clients also completed a computer-assisted self-interview, recording detailed sexual behavior, a method that has been previously shown to be reliable and acceptable (14, 15). Responses were also routinely verified by the clinician at the time of the consultation.

Laboratory methods. Men with acute NGU provided a first pass urine specimen of at least 20 ml for *C. trachomatis* and *M. genitalium* testing by strand displacement amplification (ProbeTec-ETCT amplified DNA assay; Becton, Dickinson) and PCR as described by Yoshida et al. (16), respectively. These diagnostic assays are used to deliver results to patients and clinicians and have been accredited by the National Association of Testing Authorities (NATA), Australia. Cases had ≥5 PMNL/HPF on urethral Gram stain, collected using a cotton swab moistened with normal saline, in the absence of gonococcal infection (both Gram stain and culture negative).

Study terms and definitions. In this paper "bacterial pathogen" refers to cases where *M. genitalium* or *C. trachomatis* was detected. "Idiopathic NGU" refers to cases where *C. trachomatis* and *M. genitalium* were not detected. Consistent condom use for anal/vaginal sex refers to entry in the database of 100% condom use for anal and/or vaginal sex in the prior 3 months and frequently reflected the additional practice of unprotected oral sex, which could not be dually/additionally recorded in the database. "Nonanal/nonvaginal sexual activity" refers to report of sexual partners in the previous 3 months but no anal or vaginal sexual intercourse. This indicates no penetrative anal or vaginal sex occurred in the prior 3 months and reflects mainly the practice of oral sex, which is predominantly unprotected, but may also reflect other nonpenetrative sexual practices.

Statistical analysis. Data were analyzed using SPSS version 20. Chi-square test, Fisher exact test, and univariate analysis were used to calculate *P* values and crude odds ratios (ORs) with 95% confidence intervals (95% CI), where appropriate. Demographic, behavioral, and laboratory characteristics were compared in cases with and without pathogens. Cases were stratified by sexual preference and compared by univariate and multivariate logistic regression. Where two variables were strongly correlated, only the variable most strongly associated with the outcome was included. Finally, we conducted two subanalyses comparing behavioral characteristics of MSM to MSW restricted to idiopathic cases only and then to cases where *M. genitalium* or *C. trachomatis* was detected.

Ethics. Ethical approval for this study was granted by the Alfred Hospital Ethics Department (approval number 537/11). The need for written informed consent from participants was waived for this study, as all records were anonymized and deidentified with a false unit record number attached to the clinical record prior to analysis.

RESULTS

Demographic, behavioral, and laboratory characteristics of the study population. During the study period, there were 5,452 presentations of males with acute urethral symptoms. Of these, 4,326 were first presentations with acute urethral symptoms, of which urethral Gram stains were performed in 3,053 (71%) cases. MSM were slightly more likely to have a Gram stain than MSW (OR of 1.3; 95% CI of 1.1 to 1.6), reflecting the increased risk of *Neisseria gonorrhoeae* in this population in our clinical setting. The study population was comprised of 1,295 (42%,) males who had both first presentation with acute urethral symptoms and fulfilled the laboratory criteria of greater than 5 PMNL/HPF on urethral Gram stain. The median age of participants was 31 (interquartile range [IQR], 26 to 41 years). A total of 380 (32%) cases reported ≥1 male partner in the prior 3 months (median of 3, IQR of 2 to 6), and 830 (70%) reported ≥1 female partner (median of 2, IQR of 1 to 3) (Table 1). Reported consistent condom use for anal sex (39%) was higher than for vaginal sex (14%; $P < 0.001$) in the 3 months prior to presentation. *C. trachomatis* was detected in 401 (32%; 95% CI of 29 to 34%) and *M. genitalium* in 134 (11%; 95% CI of 9 to 13%) cases. There were no time trends in pathogen detection for either *C. trachomatis* or *M. genitalium* over the 6-year study period. Overall, no pathogen was detected in 772 (59%) cases with acute NGU.

TABLE 1 Demographic, behavioral, and laboratory characteristics of the study population ($n = 1,295$)

Characteristic[a]	Value	% (IQR)
Demographic and behavioral characteristics		
Median age (yrs)	31	(26–41)
No. of participants with an MSP in the previous 3 mo		
No	809	68
Yes	380	32
Median no. of MSP in the previous 3 mo	3	(2–6)
No. of participants with an FSP in the previous 3 mo		
No	358	30
Yes	830	70
Median no. of FSP in the previous 3 mo	2	(1–3)
No. of participants with 100% condom use in those engaging in anal sex in the previous 3 mo		
No	204	61
Yes	128	39
No. of participants with 100% condom use in those engaging in vaginal sex in the previous 3 mo		
No	695	86
Yes	116	14
Laboratory characteristics (no. of participants)		
Chlamydia trachomatis		
Not detected	872	69 (66–71)
Detected	401	32 (29–34)
Unassessable/equivocal[b]	13	1
Not tested	9	1
Mycoplasma genitalium		
Not detected	1,098	89 (87–91)
Detected	134	11 (9–13)
Unassessable/equivocal[b]	3	0
Not tested	60	5

[a] MSP, male sexual partner; FSP, female sexual partner.
[b] This category represents samples that were deemed unassessable or equivocal and included samples with inhibitors, fluorescence, or insufficient specimen for testing.

Characteristics of cases with specific pathogens and idiopathic NGU. The characteristics of cases with *C. trachomatis* and *M. genitalium* were similar to each other but differed from those associated with idiopathic NGU (Table 2). Compared to cases with idiopathic NGU, *C. trachomatis*- or *M. genitalium*-positive cases were less likely to have a recent male partner ($P < 0.001$) and were more likely to report a recent female partner ($P < 0.001$). Cases with idiopathic NGU were more likely than cases with *C. trachomatis* or *M. genitalium* to report recent engagement in low-risk practices, 100% condom use for vaginal/anal sex ($P < 0.001$), or sexual practices other than penetrative anal/vaginal sex as their only recent exposure ($P = 0.002$).

The characteristics of bacterial NGU were compared to idio-

TABLE 2 Characteristics associated with specific pathogens and idiopathic NGU

Characteristic[a]	No. (%) of participants[b]			*P* value (x^2)
	C. trachomatis ($n = 401$)	*M. genitalium* ($n = 134$)	Idiopathic ($n = 772$)	
Age in yrs				
≤31	201 (50)	62 (46)	396 (51)	
>31	200 (50)	72 (54)	376 (49)	0.56
MSP in the previous 3 mo				
0	303 (81)	97 (78)	418 (60)	
≥1	73 (19)	27 (22)	282 (40)	<0.001
FSP in the previous 3 mo				
0	67 (18)	23 (19)	270 (39)	
≥1	308 (82)	101 (82)	430 (61)	<0.001
100% condom use for vaginal/anal sex in the previous 3 mo				
No	321 (88)	103 (85)	479 (74)	
Yes	45 (12)	18 (15)	167 (26)	<0.001
Nonanal/nonvaginal sexual activity in the previous 3 mo				
No	355 (95)	118 (94)	604 (88)	
Yes	19 (5)	8 (6)	79 (12)	0.002

[a] MSP, male sexual partner; FSP, female sexual partner.
[b] Missing data comprises ≤8% of data for each variable and has been excluded in calculation of percentages.

pathic NGU by multivariable analysis. Compared to cases with bacterial NGU, cases with idiopathic NGU were more likely to have consistently engaged in protected vaginal/anal sex (AOR = 1.8; 95% CI of 1.3 to 2.5), twice as likely to have had a male partner in the prior 3 months (AOR = 2.3; 95% CI of 1.7 to 3.1), and less likely to have a recent female partner (AOR = 0.4; 95% CI of 0.3 to 0.6).

Characteristics of acute NGU in MSM compared to MSW. The characteristics of MSW exclusively reporting recent female partners were compared to MSM, exclusively reporting recent

TABLE 3 Characteristics of exclusive MSM compared to exclusive MSW with acute NGU ($n = 1,139$)

Characteristic	No. (%) of participants[a]		OR[b] (95% CI)	AOR[c] (95% CI)	
	Exclusive MSW, $n = 795$	Exclusive MSM, $n = 344$		Model 1	Model 2
Age in yrs					
≤31	387 (49)	161 (47)			
>31	408 (51)	183 (53)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Pathogen detected					
C. trachomatis	300 (39)	65 (19)	0.4 (0.3–0.5)	Omitted	0.4 (0.3–0.6)
M. genitalium	97 (13)	23 (7)	0.5 (0.3–0.9)	Omitted	0.5 (0.3–0.8)
Idiopathic NGU	407 (51)	258 (75)	2.8 (2.2–3.8)	2.4 (1.8–3.3)	Omitted
100% condom use for vaginal/anal sex in the previous 3 mo					
No	678 (87)	188 (61)			
Yes	101 (13)	119 (39)	4.2 (3.1–5.8)	3.7 (2.7–5.1)	3.9 (2.7–5.4)
Nonanal/nonvaginal sexual activity in the previous 3 mo					
No	770 (98)	277 (81)			
Yes	20 (3)	64 (19)	8.9 (5.3–15.0)	8.1 (3.6–17.9)	9.1 (3.9–21.1)

[a] MSM, men who have sex with men only; MSW, men who have sex with women only. Men who reported sex with both men and women ($n = 35$) have been excluded. Missing data comprises ≤6% of data for each variable and has been excluded in calculation of percentages.
[b] OR, unadjusted odds ratio.
[c] Adjusted odds ratios (AOR) were calculated, adjusting for age, idiopathic cases, 100% condom use, and nonanal/nonvaginal sexual activity. Due to the strong inverse correlation between idiopathic cases and *C. trachomatis* and *M. genitalium*, two models have been created. Model 1 includes age, idiopathic NGU, 100% condom use, and nonanal/nonvaginal sexual activity variables. Model 2 includes age, *C. trachomatis*, *M. genitalium*, 100% condom use, and nonanal/nonvaginal sexual activity variables.

male partners (Table 3). Men reporting no sexual partners in the past 3 months ($n = 13$) and bisexual men ($n = 35$) were excluded. Due to the strong inverse correlation between the detection of bacterial pathogens and idiopathic NGU, two models were created to explore associations by multivariable analysis, the first model adjusting for idiopathic NGU and the second adjusting for the presence of *C. trachomatis* and *M. genitalium*. Compared to exclusive MSW, exclusive MSM with acute NGU were more than 8 times as likely to report sexual activity other than penetrative anal or vaginal sex (AOR = 8.0, 95% CI of 3.6 to 17.8 [model 1]; AOR = 9.1, 95% CI of 3.9 to 21.1 [model 2]) and 3 to 4 times as likely to report consistent condom use for penetrative anal/vaginal sex (AOR = 3.6, 95% CI of 2.7 to 5.0 [model 1]; AOR = 3.9, 95% CI of 2.7 to 5.4 [model 2]) in the prior 3 months. MSM were less likely to have either *C. trachomatis* (AOR = 0.4; 95% CI of 0.3 to 0.6) or *M. genitalium* (AOR = 0.5; 95% CI of 0.3 to 0.8) and more likely to have idiopathic NGU (AOR = 2.4; 95% CI of 1.8 to 3.3) than MSW. Interestingly, in a subanalysis of those infected with either *C. trachomatis* or *M. genitalium*, MSM were significantly more likely than MSW with these pathogens to report consistent protected anal/vaginal sex (OR = 4.7; 95% CI of 2.6 to 8.3). MSM with idiopathic NGU were also more likely than MSW to report protected sex (AOR = 3.5; 95% CI of 2.4 to 5.0) or sexual activity other than penetrative anal/vaginal sex as their only exposure (AOR = 5.8; 95% CI of 3.2 to 10.7) in the 3 months prior to symptom onset.

DISCUSSION

In this large sample of males with symptomatic acute NGU, clear epidemiological and laboratory differences were observed between MSM and MSW. *C. trachomatis* and *M. genitalium* were detected significantly less frequently in MSM than in MSW. MSM were more likely than MSW to report relatively low-risk behaviors prior to symptom onset, such as consistent condom use for penetrative anal sex or sexual activity other than anal intercourse with recent partners, even when *C. trachomatis* or *M. genitalium* were detected. This study provides an important insight into the contribution and relevance of low-risk sexual behaviors to acute NGU, particularly in MSM, and has implications for etiologic research efforts and prevention and management approaches for acute NGU.

While a retrospective study has limitations, it has allowed a much larger cohort to be investigated than would be possible prospectively. This is the largest published series of acute NGU, and the striking consistency with our more rigorous case-control study in pathogen detection and behavioral associations supports the validity of the findings, but with a cohort almost four times greater (2). The prevalence of pathogens identified in both studies is reassuringly similar, and these data confirm *C. trachomatis* and *M. genitalium* are less likely to be detected in MSM. The estimates for *C. trachomatis* and *M. genitalium* are also in keeping with other estimates from our service and region (17–20). It was interesting to note that even in the presence of a bacterial pathogen, MSM reported more consistent condom use for anal sex than MSW for vaginal sex and that MSM with idiopathic NGU were also substantially more likely to report engaging in only nonpenetrative anal/vaginal sexual activity with their partners in the prior 3 months. Collectively, these data suggest that MSM may be acquiring established and unidentified urethral pathogens more commonly than anticipated via low-risk sexual practices, perhaps reflecting the widespread practice of unprotected orogenital sex in MSM and also other unmeasured nonpenetrative practices that could not be captured in our study. Others have reported that MSM are more likely to use condoms than MSW (21), and previous studies have shown insertive oral sex to be a predictive factor in MSM for nonchlamydial NGU (22, 23). Sporadic case reports of oral and respiratory bacteria, such as *Corynebacterium diphtheria*, *M. catarrhalis*, and *Haemophilus* and *Streptococcus* species in acute NGU, following orogenital sex support the contribution of oropharyngeal exposure to this syndrome and require examination in case-control studies using molecular methods (9–11, 24, 25).

The concept that the spectrum of pathogens may differ between MSM and MSW is further supported by the recent findings of Manhart et al., who examined whether key bacterial vaginosis-associated bacteria (BVAB) may be causal agents of acute NGU (26). In a case-control study involving predominantly MSW, *Leptotrichia/Sneathia* species were the only BVAB significantly associated with NGU and were detected in 15% of men with idiopathic NGU (26). Other BVAB (BVAB-2, BVAB-3, Megasphera) were most often identified in cases compared to in controls but were less common. Our group has previously reported that *Gardnerella vaginalis*, a common species within the vaginal microbiota and implicated in BV, was more common in controls than in NGU cases and associated with recent penile-vaginal sex (26); and as reported by Manhart et al., no association with *Atopobium vaginae* and NGU was found (unpublished data). These data support the broader premise that exchange of pathogenic and nonpathogenic species within the genital microbiota is occurring between sexual partners, with only some agents inducing disease or symptoms in a partner, which could also be influenced by host characteristics. Clearly, metagenomic studies will expand our etiologic understanding of idiopathic NGU, but these techniques generate vast data output, and epidemiologic studies provide important insights to refine the search into probable sources of NGU and the likely spectrum of agents.

Our study had a number of limitations. First, the size and characteristics of the idiopathic NGU group are determined by the pathogens that were tested for. In line with most clinical settings, routine testing for ureaplasma species, adenoviruses, herpes simplex virus (HSV), and trichomoniasis did not occur in this study. When previously investigated at our service in a case-control study, no association between *Ureaplasma urealyticum* and acute NGU was found, although the role of specific serotypes was not investigated (2). Recent studies using molecular methods have clearly differentiated between *Ureaplasma parvum* and *Ureaplasma urealyticum*, with some studies indicating that *U. urealyticum* may be implicated in acute NGU (6, 27–29). It is possible that cases within the idiopathic NGU group may have been attributable to *U. urealyticum*, and routine testing within this large series would have been helpful in expanding knowledge regarding its association with acute NGU and its specific characteristics; however, this was not feasible within the clinical setting. Within the idiopathic NGU group, a limited number of men who presented with suggestive symptoms were additionally tested for HSV, trichomoniasis, and adenoviruses, in accordance with our clinic guidelines. Importantly, this testing was highly selective and performed in only a small number of cases ($n = 78$), yielding 2 cases of *Trichomonas vaginalis*, 8 with adenoviruses, and 8 with HSV; we have not included these data in analyses. Some insight into the likely contribution of these pathogens to the "idiopathic" group in

our current study can be derived from our previous case-control study at this service. In this study, of over 600 men, of whom 329 had acute NGU, 4% of cases were attributed to adenoviruses and HSV, while only one case and no controls had *T. vaginalis* detected by PCR (2). In Melbourne, trichomoniasis is rare, occurring in <1% of women attending our service annually (30, 31). While universal testing for these agents would have informed analyses and reduced the size of the idiopathic group, this is not part of routine care in the majority of international clinical settings, and based on these previous data we estimate up to 5% of the idiopathic group may have had adenovirus, HSV, or trichomoniasis. A final limitation is that for those who reported sexual partners but no penetrative anal/vaginal sex, and for those who reported 100% condom use for anal/vaginal sex, unprotected oral sex was not additionally/dually recorded in the database. It is the opinion of the clinician researchers in this study that the majority of these cases are likely to have engaged in the additional practice of unprotected oral sex, although other unmeasured sexual practices may have occurred.

Overall, these data suggest that MSM with acute NGU have a different etiologic spectrum from MSW that may be related to differences in sexual behaviors. Our data indicate that transmission of organisms capable of inducing acute urethral symptoms may be occurring between MSM more commonly than anticipated through relatively "low-risk" sexual practices, such as orogenital sex. These epidemiological findings have implications for management approaches to NGU and are of relevance to future research efforts in the search for etiologic agents.

ACKNOWLEDGMENTS

We would like to acknowledge and thank A. Afrizal for the extraction of data from the electronic database and A. M. Foote for his review of the manuscript.

V.S.R., C.K.F., A.W., T.H.R., G.F., M.Y.C., and C.S.B. do not have a commercial or other association that might pose a conflict of interest.

This work was not funded.

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