Etiology of symptomatic urethritis in men and association with sexual behaviors

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ABSTRACT

INTRODUCTION: Gonorrhea and chlamydia are sexually transmitted infections (STI) that are the most common causes of urethritis in men. The role of specific sexual behaviors and presentation of urethritis is often overlooked.

METHODS: Data was retrospectively reviewed on all men presenting at the major STI clinic in Providence, Rhode Island. Predictors of gonorrhea and chlamydia infection were modeled using a generalized model assuming a binary distribution.

RESULTS: Of the men with urethritis, 27% had chlamydia, 13% gonorrhea, 3% both, and 63% neither (non-gonococcal, non-chlamydial urethritis). MSM were more likely to test positive for gonorrhea than MSW (25% of MSM versus 6% of MSW; $p<0.01$).

CONCLUSIONS: MSM with urethritis were much more likely to test positive for gonorrhea which may be due to increased risk behaviors and spread within concentrated sexual networks. A large number of both MSM and MSW had non-gonococcal, non-chlamydial urethritis, which suggests the need for improved diagnostic testing.

KEYWORDS: urethritis, men who have sex with men, sexually transmitted diseases

INTRODUCTION

Urethritis is a disease characterized by urethral inflammation and is a common presentation of several sexually transmitted infections (STI). Symptoms of urethritis include discharge, dysuria, urinary frequency, pruritus and/or irritation with micturition. The most common infectious etiologies of urethritis are gonorrhea and chlamydia [1]. These two STIs account for a significant burden of disease in younger individuals with over 1.4 million cases of chlamydia and 300,000 cases of gonorrhea reported in the United States (US) in 2013 [1]. Other causes of urethritis include different bacterial pathogens, viral pathogens, parasitic pathogens and non-infectious causes [2-4]. A significant number of urethritis cases are often due to non-gonorrheal, non-chlamydial (NGNC) infections [5, 6]. The etiology of urethritis may also differ by sexual behavior [7, 8]. Men who have sex with men (MSM) are a group disproportionately affected by HIV and other STIs [9, 10]. Men who specifically have anal sex with other men may be at risk of other urogenital pathogens that could potentially cause urethritis other than gonorrhea and chlamydia [10]. It is the goal of this study to determine if the etiologies of urethritis according to different sexual behaviors are likely to predict the incidence of NGNC infections.

MATERIALS AND METHODS

Study Sample

A retrospective study was performed on all men presenting to the only publicly funded STI Clinic at The Immunology Center at The Miriam Hospital in Providence, Rhode Island (RI) from January 2012 to May 2014. Upon presentation to the clinic, all individuals complete a one-page assessment of demographics and behaviors used for surveillance and reporting purposes. Behavioral questions included number of sex partners in the past 12 months (oral, vaginal, and anal sex), number of HIV positive partners, number of partners with condomless sex, number of partners who were intravenous drug users (IDU), history of a prior STI, and anonymous partners. Men that had sex with men only and men that had sex with men and women were considered as MSM. Men who had sex with only women were considered MSW. All patients submitted first-void urine specimens for the purpose of *N. gonorrhoeae* and *C. trachomatis* testing via nucleic acid amplification tests (NAAT) using the Hologic Gen-Probe TIGRIS, APTIMA assay®.

Statistical Methods

All analyses were conducted using SAS Software 9.4. Predictors of interest for gonorrhea and chlamydia status were modeled using a generalized model assuming a binary distribution with sandwich estimation. Predictors of interest include sexual behavior (MSM/MSW), number of sexual partners in the last year, history of STI in last year and in lifetime, and presence/absence of urethritis symptoms of dysuria and discharge. When no significant interaction between the predictors of interest was found, the results for each group were examined. Differences between groups were assessed using a two-sample proportions test and independent sample t-tests. Alpha was set *a priori* at 0.05 level and all confidence intervals are set at the 95% level.

RESULTS

During the study period a total of 1081 male patients presented for STI testing. The geographic distribution of patients included Rhode Island 92%, Massachusetts 5%, Connecticut 1%, and other 2%. The median age was 30 years (range 15-74 years, SD 11.6, inter-quartile range (IQR) 15). The distribution of race included White/Caucasian 69%, Black/African American 20%, Asian 3%, and other 7%. Hispanic/Latino patients comprised 22% of the population. In terms of sexual behavior, 39% (423/1081) of patients identified as being MSM, 59% (643/1081) of patients identified as being MSW and 1% (13/1081) of patients identified with other sexual behaviors or their behaviors were unknown. The average and median numbers of sexual partners in the overall sample were 5.2 and 3.0 partners (SD 7.1, IQR 4), respectively. Of all patients tested, 3% (31/1081) tested positive for gonorrhea, 9% (102/1081) patients tested positive for chlamydia, and 1% (7/1081) tested positive for both. Patients who were symptomatic with urethritis comprised 11% (119/1081) of the sample. Patients who comprised the 962 not meeting the criteria for urethritis were asymptomatic and returning to clinic for concern of subclinical infection, or had symptoms that were not related to urethritis. (**Table 1**)

Behavior as a predictor of STI, with and without urethritis

The odds of gonorrhea were 9.4 times (95% CI [4.4, 20.1]) higher for those with urethritis compared with those without urethritis, p<0.01. Of those with urethritis, the odds of gonorrhea were 4.9 (95% CI [1.5, 15.8]) times higher for MSM compared with MSW, p<0.01. Of those without urethritis, the odds of gonorrhea were not significantly different, p=0.20.

In addition, the odds of chlamydia were 4.6 (95% CI [2.8, 7.4]) times higher for those with urethritis compared with those without urethritis, p<0.01. Interestingly, of those with urethritis, the odds of chlamydia were not significantly different for different sexual behaviors, p=0.23.

In addition to sexual partner preference, lifetime and recent STI history and number of sexual partners were also examined. Of those with urethritis, lifetime history of STI was not predictive of gonorrhea, p=0.65, though the odds of gonorrhea were 3.6 times (95% CI [1.1, 12.4]) higher for those with a 12 month history of an STI compared to those without this history, p=0.04. Number of partners in the last 12 months was not predictive of gonorrhea, p=0.10 or chlamydia, p=0.41.

Table 1. Men with Symptomatic Urethritis

	MSM (N=40)	MSF (N=79)	P value (0.094)
Age			
Average	34 ±12.2	32 ±10.1	0.344
Range	16-31	16-58	
Race			
Asian	5% (2)	3% (2)	1.000
Black or African American	23% (9)	27% (21)	0.663
White/Caucasian	64.3% (26)	57% (45)	0.435
Other	8% (3)	5% (4)	0.686
Ethnicity			
Hispanic or Latino	3% (1)	27% (21)	0.001
Health Coverage			
Medically Insured	23% (9)	18% (14)	0.624
Self-assessed risk of contracting HIV			
Low	20% (8)	37% (29)	0.093
Medium	28% (11)	10% (8)	0.019
High	8% (3)	3% (2)	0.333
(+) HIV test in the past	25% (10)	1% (1)	<0.001
Sexual Behavior			
100% Condom use for anal/ vaginal sex	10% (4)	25% (20)	0.056
Total sex partners in 12 months	9.4 ±13.2	3.6 ±3.2	<0.001
Partners known to have HIV/ IV Drug use	23% (9)	0% (0)	<0.001
Number of partners with unprotected sex	7.5 ±13.8	2.0 ±2.5	<0.001
STI in past the past 12 months	20% (8)	11% (9)	0.268
Lifetime incidence of an STI	45% (18)	39% (31)	0.561
Injection drug use	10% (4)	1% (1)	0.043
Average days with symptoms before evaluation	17 ±44.9	35 ±77.	
Symptoms			
Dysuria	70% (28)	66% (52)	0.685
Irritative urinary symptoms	1% (2)	15% (12)	0.137
Discharge	50% (20)	46% (36)	0.700
Dyspareunia	0% (0)	3% (2)	0.550
Urinary frequency	8% (3)	4% (3)	0.403
Urine PCR			
(+) Gonorrhea	25% (10)	6% (5)	0.007
(+) Chlamydia	20% (8)	30% (24)	0.277
NGNCU	60% (24)	65% (51)	0.690

MSM, men who have sex with men
MSF, men who have sex with women only
HIV, human immunodeficiency virus
STI, sexually transmitted infection
PCR, polymerase chain reaction (described in methods)
NGNCU, non-gonorrheal non-chlamydial urethritis

Symptoms as a predictor of STI

Of those with urethritis, dysuria was not predictive of chlamydia or gonorrhea, p=0.51 and p=0.27, respectively. Likewise, discharge was not predictive of chlamydia, p=0.23. However, discharge was predictive of gonorrhea, p=0.0047. Specifically, odds of having gonorrhea were 9.2 (95% CI [2.0, 43.0]) times higher for those with discharge compared with those without discharge.

DISCUSSION

Urethritis is a common male presentation to clinics which specialize in STIs or men's health. By identifying sexual behaviors, clinicians may be able to provide counseling as well as aid in the diagnostic work-up of urethritis, however these findings aid in completing a holistic picture rather than suggest a modification in practice.

Differences in sexual behaviors may contribute to the variety of pathogenic etiologies in men with urethritis. There is evidence to suggest that sexual networks facilitate the spread and persistence of certain STIs [11, 12]. Studies show that MSM have higher rates of gonorrhea in general [13]. The results of this study further corroborate these numbers and demonstrate that MSM with urethritis have four times the odds of gonorrhea compared with MSW. Differences in anal flora compared to vaginal flora may predispose or facilitate development of different pathogens compared to MSW, however more research is necessary regarding this theory [13]. This theory may spur further motivation for diagnostic evaluation of extragenital sites, such as rectal NAAT for known STI [14].

Despite *neisseria gonorrhoeae* and c*hlamydia trachomatis* being the most common causes of urethritis in men, we found a significant number of NGNC cases [2, 15]. This can present a significant challenge for medical providers and specialists. Patients diagnosed with NGNC urethritis oftentimes present to urologists, and without a high degree of suspicion for other pathogens, a potential curable etiology may be missed. Using highly sensitive conventional diagnostic testing, detection rates of gonorrhea in symptomatic patients are approximately 20% while rates of chlamydia range from 15-30% [18]. Given this study and existing literature, it is important to consider alternative diagnostic tests, which further characterize urethritis. In some men, no etiology of urethritis can be found despite intensive work-up.

Understanding the wide range of differences in behaviors and lifestyles of patients is important to identify potential etiologies of urethritis and other diseases. This study further demonstrates that there are, in fact, significant behavioral differences between MSM and MSW in terms of number of sexual partners and condomless sex. It is clear from the literature that high-risk sexual behaviors and lifestyles predispose patients to repeat STI, HIV, and other poor health outcomes [19]. Counseling and education would benefit men with urethritis and risk regarding HIV acquisition; all men who present with urethritis or are diagnosed with an STI should be screened for HIV [20].

Limitations

Although this study used a consistent definition of urethritis by utilizing symptomatic measures, objective measures were not used (WBC on urethral swab, first-void urine, or discharge on physical exam). Distinguishing between UTI and urethritis without a urine analysis, urethral smears, or urine cultures may have led to inappropriate characterization as urethritis. The retrospective nature of the study also limited associations that could be made between the outcomes of interest and demographic and behavioral data. In addition, a selection bias may exist for our data, given that patients presented to an STI clinic, instead of their primary care physician or urologist; thus our scope of inference is limited to those presenting to an STI clinic.

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