

The Presence or Absence of Symptoms Among Cases of Urethral Gonorrhoea Occurring in a Cohort of Men Taking Human Immunodeficiency Virus Pre-exposure Prophylaxis in the PrEPX Study

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We aimed to estimate how often urethral gonorrhoea is symptomatic among men in the Pre-Exposure Prophylaxis Expanded Victoria study. Eighty-seven percent of 213 cases of urethral gonorrhoea were symptomatic. Ensuring men with urethral gonorrhoea both recognize and present early for treatment is critical to reduce transmission.

Keywords. gonorrhoea; men who have sex with men; screening; sexually transmitted infection; urethritis.

Studies that have attempted to determine the proportion of men who develop symptoms after infection of the urethra with *Neisseria gonorrhoeae* have been subjected to considerable potential bias. Apart from one cohort analysis undertaken approximately 50 years ago, these cross-sectional studies have either been retrospective descriptions from sexual health clinics or studies screening large numbers of men [1–7]. Studies in sexual health clinics are biased towards overestimating the proportion of patients with symptoms because men who develop symptoms preferentially attend these services [8]. These clinic-based studies have estimated that 89%–94% of men with urethral *N gonorrhoeae* develop symptoms [1–3]. One cohort analysis among service men in 1974 found that 98% of men with urethral

gonorrhoea developed symptoms [7]. In contrast, screening studies are biased towards underestimating the proportion of patients with symptoms because cases with symptoms have a much shorter duration and therefore are less likely to be present in cross-sectional studies. Furthermore, these screening studies have primarily screened asymptomatic men (ie, reporting that between 0% and 58% of men have symptoms) [4–6].

Estimating the proportion of men who have symptoms from urethral gonorrhoea is important because the recognition of symptoms prompt individuals to access healthcare and treatment. This allows for other important steps, such as contact tracing, which can put substantial downward pressure on transmission within populations. However, if symptoms are uncommon among men with urethral gonorrhoea, then strategies that increase symptom recognition will be less effective in reducing transmission, whereas strategies that promote regular asymptomatic screening of men at risk may be preferred.

We recently undertook a large cohort study of participants taking pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) in which 233 cases of urethral gonorrhoea occurred [9]. Data from this cohort study should provide a less biased method of determining the proportion of symptomatic cases than previous studies because participants were required to attend PrEP appointments every 3 months and sexually transmitted infection (STI) screening was required of all participants regardless of the presence of symptoms. Participants were also asked to attend their study enrollment clinic for testing and treatment should they develop STI symptoms between quarterly visits. The present study aimed to determine the proportion of men with symptomatic urethral gonorrhoea from the cohort study.

MATERIALS AND METHODS

The Pre-Exposure Prophylaxis Expanded (PrEPX) Victoria study was a multisite, single-armed, open-label intervention study of tenofovir disoproxil fumarate and emtricitabine for HIV PrEP among 4275 participants in Victoria, Australia, between July 2016 and May 2018 [9]. Men were followed up every 3 months. We conducted a retrospective analysis of the clinical records of men with linked STI testing data who developed incident urethral gonorrhoea and urethral chlamydia during the 3185 person-years of follow up in the PrEPX study. A detailed description of the PrEPX study is published elsewhere [10]. A total of 2981 PrEPX participants enrolled through 1 of 5 recruitment sites that also participate in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) project, an existing sentinel surveillance network [11], and were monitored for STI outcomes during study follow up.

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PATIENT CONSENT STATEMENT

Ethics approval was obtained from the Alfred Hospital Human Research Ethics Committee for the PrEPX study (projects 100/16 and 248/17) [10]. All participants provided written consent to have their medical records reviewed as part of this project when they consented to the PrEPX study.

Participants who had a positive test result from a urethral swab or first pass urine specimen for *N gonorrhoeae* by nucleic acid amplification test at 1 of the 5 recruitment sites were included in this analysis. As previously described [10], the ACCESS system uses specialized data extraction software to routinely extract clinical data from patient management systems. These data identified each case of urethral gonorrhoea among participants in the PrEPX study. Chart review for all urethral gonorrhoea cases was performed by L.C.D. and E.T.A. We reported the frequency, proportion, and corresponding 95% confidence intervals of urethral symptoms and other clinical characteristics. All statistical analyses were conducted using Stata (version 14).

RESULTS

Between July 2016 and May 2018, 233 cases of urethral gonorrhoea were diagnosed among 191 individual men. Table 1 shows the characteristics of the 191 men. Of the 191 men, 160 individuals were diagnosed with a single infection, 24 with 2

infections, 5 with 3 infections, 1 with 4 infections, and 1 with 6 infections during the study period (Table 2).

A total of 8 cases were excluded from this analysis because 2 cases (1 participant) had been excluded from the PrEPX study at enrollment after HIV was diagnosed and 6 cases did not have information on urethral symptoms in their clinical notes.

Of the 225 cases included, 176 reported urethral symptoms on the day of testing and 49 reported an absence of symptoms. Of the 176 cases who had urethral symptoms, 139 had typical urethral discharge (yellow, green, or pus like) and 30 had other urethral symptoms such as urethral discomfort, dysuria, or a nonpurulent discharge.

Among the 225 cases of urethral gonorrhoea, 222 were also tested for urethral chlamydia on the same day. Of these 222 cases of urethral gonorrhoea, 35 were coinfecting with urethral chlamydia. Of the 174 symptomatic cases, 29 (17%) were also coinfecting with chlamydia. Of the 48 asymptomatic cases, 6 (13%) were also coinfecting with chlamydia.

Among the 49 cases that were asymptomatic, 7 were treated on the day of testing because they were sexual contacts of a known case of gonorrhoea. Of the 42 untreated asymptomatic cases, 37 had a record of them returning for treatment at 1 of the 5 recruitment sites and 5 sought treatment with a local healthcare provider. Among the 37 asymptomatic cases who returned for treatment, the time between testing and

Table 1. Characteristics of Participants With Urethral Gonorrhoea (N = 191)

Characteristics	No. (%)
Age (years), mean (standard deviation)	36.0 (10.1)
Gender	
Male	189 (99.0)
Transgender, Male	1 (0.5)
Nonbinary/Gender Fluid	1 (0.5)
Sex at Birth	
Male	189 (99.0)
Female	2 (1.0)
Sexuality	
Gay/Homosexual	180 (94.2)
Bisexual	9 (4.7)
Other	2 (1.0)
Country of Birth	
Australia	100 (52.4)
Overseas	68 (35.6)
Missing	23 (12.0)
Injecting Drug Use at Enrollment	
Yes	17 (8.9)
No	174 (91.1)
In the 3 Months Before Enrollment:	
Any condomless receptive anal intercourse with a casual male partner with HIV or of unknown HIV status	99 (51.8)
>1 Episode of condomless insertive anal intercourse with a casual male partner with HIV or of unknown HIV status	82 (42.9)
>1 Episode of anal intercourse without correct and consistent condom use (eg, condom slipped off or broke)	59 (30.9)
Used methamphetamines	36 (18.8)
Self-reported diagnosis of rectal gonorrhoea, rectal chlamydia, or syphilis	48 (25.1)

Abbreviations: HIV, human immunodeficiency virus.

Table 2. Characteristics of 225 Cases of Urethral *Neisseria Gonorrhoeae* in the PrEPX Study

Characteristics	n/N	% (95% CI)
On Initial Presentation:		
Urethral Symptoms Present	176/225	78 (72–83)
Coinfected with urethral chlamydia*	29/174	17 (11–23)
Typical urethral symptoms	139/176	79 (72–84)
Other urethral symptoms†	30/176	17 (12–23)
Urethral Symptoms Absent	49/225	22 (17–28)
Coinfected with urethral chlamydia‡	6/48	13 (5–25)
Asymptomatic and treated on day	7/49	14 (7–27)
Asymptomatic and not treated on day	42/49	86 (72–93)
Known contact of gonorrhoea infection	21/225	9 (6–14)
Initially Asymptomatic and Returned for Treatment		
Returned to recruitment site for treatment	37/42	88 (75–95)
Urethral symptoms absent	16/37	43 (29–59)
Urethral symptoms present	9/37	24 (13–40)
Data incomplete to determine symptoms	12/37	32 (20–49)
Symptomatic at either presentation§	185/213	87 (82–91)

Abbreviations: CI, confidence interval; PrEPX, Pre-Exposure Prophylaxis Expanded.

*Two men with urethral symptoms were not tested for urethral chlamydia and therefore were excluded for coinfection analysis.

†The data on the nature of the symptoms was missing for 7 participants.

‡One man who did not have urethral symptoms was not tested for urethral chlamydia and therefore was excluded for coinfection analysis.

§The denominator excluded 7 asymptomatic individuals who were treated on the day of testing (contacts of gonorrhoea) and 5 who did not return for treatment at the 5 recruitment sites.

treatment follow up ranged from 2 to 16 days (mean = 6, median = 5 days). Nine had documentation that they had since developed some urethral symptoms, 12 cases had no documentation as to whether they were symptomatic or not, and 16 remained asymptomatic.

If the proportion of cases with symptoms includes the 176 who initially had symptoms and the 9 who later developed symptoms, then the proportion of cases with symptoms was 87% (185 of 213) (12 excluded because 7 asymptomatic cases were treated on the day of testing and 5 did not return for treatment at a recruitment site).

DISCUSSION

In this cohort study of men taking PrEP, 87% of men who acquired urethral gonorrhoea developed symptoms. This finding is relatively consistent with the estimates from most of the clinic-based studies where between 89% and 94% of men were symptomatic [1–3] and the only other cohort study where 98% of infections were symptomatic [7]. However, our findings are substantially greater than the screening studies where between 0% and 58% were symptomatic [4–6].

One of the strengths of this study is that we have managed to capture participants at 3 monthly intervals and also when symptomatic. Due to the design of this study, we have been able to combine the strengths of previous sexual health clinic studies and those of screening studies.

There are several limitations to our study. First, the data on symptoms were collected retrospectively from patient records. More importantly, however, only a few cases did not specifically mention either the presence or absence of urethral symptoms. Second, our study may have slightly overestimated the proportion of cases who were asymptomatic because 7 asymptomatic cases who were contacts of gonorrhoea were treated on the day and may have developed symptoms if they had not been treated so promptly. We may have also underestimated the proportion of men who would have developed symptoms because some men were recalled and treated within a short time frame of only a few days (median = 5 days). The cases of chlamydia coinfection may have also affected our results. Approximately 17% of the symptomatic cases were coinfecting, and therefore some of these symptoms may be attributable to the chlamydia infection rather than the gonorrhoea infection.

Previous studies of men attending sexual health clinics have reported slightly higher rates of symptomatic urethral gonorrhoea. Ong et al's [1] study of 242 men who have sex with men (MSM) attendances at a sexual health clinic in Melbourne found that 89% of urethral gonorrhoea cases were symptomatic. Barbee et al's [2] case-control study of 1604 MSM attending 2 sexual health clinics in the United States found that 94% of urethral gonorrhoea cases were symptomatic. Martín-Sánchez et al's [3] study of 116 heterosexual men attending a sexual health clinic in Melbourne found that 94% of cases of urethral gonorrhoea were symptomatic. Most of these sexual health clinics have a standardized reporting form that allows for more complete sets of data. However, the nature of sexual health clinics creates a bias towards more symptomatic cases given that individuals with symptoms are prompted to attend these services by the symptoms [12].

The reported proportion of men who are symptomatic with urethral gonorrhoea varies greatly in previous screening studies. In Pack et al's [5] study of black male adolescents from detention facilities in the United States, 0 of 19 cases of urethral gonorrhoea reported symptoms. However, the study also reported 9 cases of dual chlamydia/gonorrhoea urethral infection in which 33% of males were experiencing symptoms so it is possible that 3 of 28 (11%) had symptoms. A study of 12 young men attending health centers and educational settings in the United States found that 58% of men with urethral gonorrhoea had symptoms [4]. The study included men with incidental urethral symptoms but actively excluded men who were seeking health-care with genitourinary symptoms as their primary reason of attendance. A further study by Handsfield et al [6] of 59 men serving in the US Army reported that 32% of men with urethral gonorrhoea had symptoms. These studies have all looked at populations that were not presenting with symptoms or actively excluded symptomatic presentations, and therefore they may have biased the findings to underestimate the numbers of symptomatic infections. They are also limited by their sample

sizes, which are significantly smaller than the sexual health clinic studies. The study design of these screening studies and low sample sizes may explain why their results have differed so greatly with the results of our study.

The estimate in our cohort analysis was much closer to the previous single cohort study and the clinic studies than it was to the cross-sectional studies. This is likely to be because if most urethral gonorrhoea cases are symptomatic (ie, finding from our study), then any estimate will be driven mostly by these cases and not the small number of asymptomatic cases. The small number of studies providing asymptomatic cases may reflect how uncommon asymptomatic cases are and therefore pragmatically how difficult it is to undertake studies to identify them.

CONCLUSIONS

Our results support previous findings that the majority of men with urethral gonorrhoea are symptomatic; however, there were a clinically meaningful number of asymptomatic presentations. These findings support health promotion to improve symptom recognition and the provision of accessible sexual healthcare but also support the need for ongoing screening in asymptomatic high-risk groups. Gonorrhoea infection occurs commonly in other sites (ie, oropharynx and anorectum) apart from the urethra. Oropharyngeal and anorectal gonorrhoea infections are mostly asymptomatic, whereas urethral gonorrhoea infections are mostly symptomatic; therefore, a combination of frequent screening and symptoms awareness are important for gonorrhoea prevention and control.

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