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***Mycoplasma genitalium* Compared to Chlamydia, Gonorrhea and Trichomonas as an Etiologic Agent of Urethritis in Men Attending STD Clinics**

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Abstract

Objectives—This purpose of this study was to investigate prevalence of *M. genitalium*, *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* in men, frequency of coinfections, and relationships among organisms with urethritis in men.

Methods—This was a cross-sectional study of 290 men (age range 19–34 yr) attending Baltimore City STD Clinics. *M. genitalium*, *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis*, during 2004 were detected using nucleic acid amplification tests (NAATs). (N = 153 with urethritis and 137 without urethritis). Demographic characteristics and risk factors were ascertained.

Results—The overall prevalences of infection with *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, and *M. genitalium*, were 20.3%, 12.8%, 3.4%, and 15.2% respectively. Prevalences in men with urethritis were 32.7%, 24.2%, 5.2%, and 22.2% for *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, and *M. genitalium*, respectively. Percentages of coinfections were high. All men with *N. gonorrhoeae* had urethritis. *C. trachomatis* and *M. genitalium* were found to be significantly associated with urethritis in univariate analysis and in multiple logistic regression analysis.

Conclusion—The association of *M. genitalium* with urethritis in this study provides confirmation of the importance of screening men for *M. genitalium* as a cause of non-gonococcal urethritis and supports treatment considerations for urethritis for agents other than gonococci and chlamydia.

Short Summary—Men attending STD clinics were found to have high prevalences of *M. genitalium* (MG), *C. trachomatis* (CT), and *N. gonorrhoeae* (NG); moderate prevalence of *T. vaginalis*. MG was associated with urethritis in addition to NG and CT.

Keywords

Urethritis; *Mycoplasma genitalium*; *Chlamydia trachomatis*; *Neisseria gonorrhoeae*; *Trichomonas vaginalis*; STD; Nucleic Acid Amplification Tests

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Contributors: CAG was responsible for overall design and implementation of the study, wrote the manuscript. NM conducted the data analysis and participated in writing the manuscript. AH and JH performed all the laboratory assays and assisted with data collection and data analysis. TQ participated in the study design and assisted in manuscript preparation.

Competing Interest: GenProbe, Inc. provided free test kits for this study.

Introduction

Urethritis is characterized by inflammation of the urethra and is often, but not always, caused by sexually transmitted pathogens. *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV), *Mycoplasma genitalium* (MG), adenovirus, and HSV-1/2 have been implicated as potential agents of urethritis.^{1,2}

Diagnosis is complicated because urethritis can have both infectious and non-infectious origins, including trauma.² Non-chlamydial, non-gonococcal (NCNGU) represents a challenge in diagnosis.³ There is evidence of the contribution of MG to urethritis.¹ Advances in highly sensitive and specific nucleic acid amplification tests allow better detection of organisms. We determined individual and combined contributions of CT, NG, MG, and TV to urethritis in men attending STD clinics.

Materials and Methods

292 male subjects enrolled at STD clinics to evaluate microbial etiologies of urethritis with written informed consent. The study was approved by the Western Institutional Review Board (IRB) for Johns Hopkins University and the Baltimore City Health Department IRB. Subjects were approached using random assignment of every 5th patient to the research clinician. The acceptance rate was estimated to be >85%. Sociodemographic information, symptoms, behavioral risk factors, and STD history were obtained.

All subjects received clinical standard of care. Urine and two urethral swabs were collected. A gram stain smear was prepared and urine was tested by Aptima Combo2, (GenProbe®, San Diego, CA) for CT and NG.⁴ Research TV and MG PCRs were performed on urine,⁵⁻⁷ as well as GenProbe TMA targeting TV rRNA⁵ and Gen-Probe TMA research assay targeting MG rRNA.⁸ Both research and TMA assays were required to be positive for the patient to be considered infected with TV or MG.

Urethritis was diagnosed if the gram stain demonstrated >5 PMNs/oil-immersion field. Data analyses were performed using SAS (9.1, Cary, NC). Chi square tests (p-value <0.05 for significance) and multiple logistic regression models were used to examine the association of CT, NG, TV, and MG with urethritis. Possible *a priori* confounders included age and infected partner contact. Two-way interactions were evaluated. See web-only supplemental repository for more details.

Results

Of 292 men enrolled, specimens were available for analysis for 290: 153 (52.8%) were classified as having urethritis and 137 (47.2%) without urethritis; 56.6% (164/290) reported symptoms. Reasons for visit included: symptoms (68%), “checkup” (23%), and “infected partner contact” (14%).

The mean age of the study participants was 26.9 ± 7.6 years; 96.9% were Black. Men attending one clinic were more likely have urethritis (59.2% versus 47.5%, $p=0.05$). Men referred as “contacts” were more likely to have urethritis (18.3% versus 10.2%, $p=0.05$). Men with urethritis were more likely to be symptomatic than those without (66.7% versus 45.3%, $p<0.001$). All men with gonorrhea were symptomatic. Reported symptoms (discharge, dysuria, and/or itching) were significantly associated with urethritis (OR, 2.41; 95% CI, 1.50-3.89, $p<0.001$). Education, employment status, tobacco use, condom use, new partner, and prior STDs were not significant.

The overall prevalence for CT, NG, TV, and MG were 20.3%, 12.8%, 3.4%, and 15.2%, respectively. The prevalence for each organism was always greater in those participants with urethritis (32.7%, 24.2%, 5.2%, and 22.4% for CT, NG, TV, and MG, respectively) than those without urethritis (6.6%, 0%, 1.5%, and 7.3% for CT, NG, TV, and MG, respectively).

Coinfections with additional organisms ranged from 30-40%. The percentage with coinfections was greater in men with urethritis. At least one organism was detected in 67.3% of men with urethritis versus 14.6% without urethritis. In men with urethritis, 5.9% were coinfecting with CT and MG. The same percentage was coinfecting with CT and NG. Coinfection rates of other combinations were <1%. Without urethritis, coinfection was 0.7%.

Univariate analysis demonstrated the association of organisms with urethritis (Table 1). Men infected with CT were almost seven times as likely to have urethritis as those not CT infected. Infection with MG was three times as likely in men with urethritis. There was no significant association of TV with urethritis (Table 1), or age. Participants who were “contacts” were twice as likely to have urethritis (Table 1).

Two models were fit using multiple logistic regression (Table 1). One model contained the organisms CT, NG, TV, and MG as the independent variables; the other included age and contact referral as potential confounders. No significant interactions were found. NG could not be included in modeling due to a zero in a response cell; all NG infected men had urethritis. CT and MG were strongly associated with urethritis (OR, 6.92 and OR, 3.67, respectively), but TV was not ($p=0.08$). Because of possible impact of coinfections, similar analyses were performed using data from those infected with one organism, but provided the same conclusions. A model containing 2-way interaction terms for all of the organism pairs demonstrated no terms were significant. See web-only supplemental repository for more results.

Discussion

This study is unusual in that the prevalence of CT, NG, TV, MG, and coinfections, and their association with urethritis were examined in the same study population using prospectively collected specimens. The prevalence of CT, TV, and MG in men with urethritis was similar to that reported by others in this and other STD clinics.⁹⁻¹⁰

We also found high coinfection rates of MG with NG and CT. Our coinfection rate was lower than Mena et. al., but similar or higher than reported by others.^{11,12} The rate of coinfection in subjects with urethritis with at least one pathogen was >30%, compared to 10% for those without urethritis. Our gold standard of having 2 positive tests for MG did not appear to affect the overall positivity rate, since there were only five positive tests that were not positive in both assays. (Kappa, 0.937).

In men with urethritis, 18.3% were “contacts” whereas in men without urethritis 10.2% were “contacts” ($p=0.05$). Participants who were contacts may have been asymptotically infected with the organism. Men with CT, NG, or MG were more likely to have urethritis in univariate analysis. Bradshaw et. al. reported an increased likelihood of CT and MG in men with NGU (20% versus 3% for CT and 9% versus 1% for MG).¹³ Our study corroborated those findings of significant associations of CT and MG with urethritis or NGU. We did not find an association of TV with urethritis, perhaps due to our low prevalence (3.4%). Requiring 2 positive tests for TV did not appear to affect the overall positivity rate, as only four tests were not positive in both assays (Kappa, 0.826). Our multiple logistic regression model showed CT and MG were significantly associated with urethritis ($p<0.001$). All GC infected men had urethritis. Our data confirm other studies reporting the association of CT and MG with urethritis and NGU.¹⁰⁻¹³ Because men with MG were almost four times as likely to have urethritis, the important

implication of our study may be that men need to be screened for MG, as well as NG and CT. The high prevalence of MG as a single pathogen in 14.4% of men with urethritis also conveyed significant public health implications for making diagnostic changes in the way clinics deal with urethritis and treatment¹⁵ Our limitations included not being able to enroll larger numbers of men with urethritis. Strengths included using the NAATs for four organisms concurrently, thereby identifying coinfections. In conclusion, all of the pathogens except TV were associated with urethritis in men. The association of MG with urethritis in this study confirms the importance of routinely screening men for MG as a cause of urethritis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Univariate Analyses and Two Multiple Logistic Regression Models for Association of Organisms with Urethritis

	N=153 Urethritis +	N=137 Urethritis -	Univariate		Model 1 - MLR		Model 2 * - MLR	
			OR	95% C.I.	p-value	OR	95% C.I.	p-value
CT	32.7	6.6	6.90	(3.24 - 14.70)	<0.001	6.92	(3.21 - 14.90)	<0.001
NG	24.2	0						
TV	5.2	1.4	3.72	(0.78 - 17.85)	0.11	4.29	(0.84 - 21.82)	0.08
MG	22.4	7.3	3.66	(1.73 - 7.73)	<0.001	3.67	(1.69 - 8.00)	<0.001
Age ≤ 25	54.9	52.6	1.10	(0.69 - 1.75)	0.69			
Reason for Visit = Contact	18.3	10.2	1.97	(0.99 - 3.92)	0.05	0.9	(0.54 - 1.49)	0.67
						0.95	(0.42 - 2.12)	0.90

* Model 2 also included age < 25 yr and being a contact as a reason for clinic visit