



Demographics, Clinical, and Microbiological Characteristics of Men with Urethritis in Cyprus

Kıbrıs'taki Erkek Üretritlerinin Demografik, Klinik ve Mikrobiyolojik Özellikleri

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ABSTRACT

Objective: Urethritis is a common sexually transmitted disease (STD) in developing countries; however, up to 40% of cases have no determined etiology. The characteristics of STDs vary geographically. This study aimed to define the demographic, clinical, and microbiological features of men with urethritis in Cyprus, where current data in the literature are lacking.

Methods: We included 138 patients who sought care at a university hospital in Cyprus from 2017 to 2021 and had symptoms suggestive of urethritis or a history of a recent sexual partner with STD. Urethral swab samples of the patients were tested for seven pathogens (*Trichomonas vaginalis*, *Neisseria gonorrhoeae* (*N. gonorrhoeae*), *Chlamydia trachomatis* (*C. trachomatis*), *Ureaplasma urealyticum* (*U. urealyticum*), *Ureaplasma parvum* (*U. parvum*), *Mycoplasma genitalium* (*M. genitalium*), *Mycoplasma hominis* (*M. hominis*) by multiplex polymerase chain reaction assay. In addition, demographic, clinical, and microbiological data were obtained from the hospital program and analyzed.

Results: Pathogens were detected in 59.4% of the cases: *U. urealyticum* in 26.8%, *C. trachomatis* in 13%, *N. gonorrhoeae* in 9.4%, *U. parvum* in 10.1%, *M. genitalium* in 10.1%, and *M. hominis* in 10.9%, with multiple microorganisms detected in 18.1%. Overall, 80.4% of the cases were symptomatic at presentation, and pathogen detection was associated with a history of STD, multiple sexual partners, and unprotected sexual intercourse.

Conclusions: Urethritis is a common and heterogeneous clinical condition. *U. urealyticum* dominates male urethritis in Cyprus, yet many individuals have no detectable microorganisms. Future studies should focus on developing more comprehensive quantitative molecular diagnostic methods with determined cycle threshold values to shed light on the pathogenic roles of commensal microorganisms.

ÖZ

Amaç: Gelişmekte olan ülkelerde sık görülen cinsel yolla bulaşan hastalıklardan (CYBH) olan üretritlerin önemli bir kısmında (yaklaşık %40) hala etken patojen saptanamamaktadır. CYBH ve bunlara sebep olan etkenlerin dağılımı coğrafi bölgelere göre de değişkenlik gösterebilmektedir. Biz bu çalışmada Kıbrıs'ta cinsel aktif erkeklerde üretritlerin demografik, klinik ve mikrobiyolojik özelliklerini tanımlamayı amaçladık.

Yöntemler: Çalışmaya Kıbrıs'ta yer alan bir üniversite hastanesine 2017-2021 yılları arasında üretrit semptomları ile ya da partnerinde CYBH öyküsü ile başvuran hastalar dahil edildi. Üretral swab örneklerinden multipleks polimeraz zincir reaksiyonu yöntemiyle yedi farklı mikroorganizma (*Trichomonas vaginalis*, *Neisseria gonorrhoeae* (*N. gonorrhoeae*), *Chlamydia trachomatis* (*C. trachomatis*), *Ureaplasma urealyticum* (*U. urealyticum*), *Ureaplasma parvum* (*U. parvum*), *Mycoplasma genitalium* (*M. genitalium*), *Mycoplasma hominis* (*M. hominis*)) kalitatif olarak tarandı. Hastaların demografik, klinik ve mikrobiyolojik analizlerine hastane veri tabanından ulaşıldı.

Bulgular: Örneklerin %59,4'ünde en az bir mikroorganizma tespit edildi. %26,8'inde *U. urealyticum* %13'ünde *C. trachomatis* %9,4'ünde *N. gonorrhoeae*, %10,1'inde *U. parvum*, %10,1'inde *M. genitalium* ve %10,9'unda *M. hominis* saptanırken %18,1'inde birden fazla mikroorganizma saptandı. Olguların %80,4'ünün semptomatik olduğu ve mikroorganizma varlığının geçirilmiş CYBH, birden fazla cinsel partner ve korunmasız cinsel ilişki ile bağlantılı olduğu görüldü.

Sonuç: Yaygın ve heterojen bir klinik durum olan üretritlerde Kıbrıs'ta *U. urealyticum* en sık görülen mikroorganizma olarak karşımıza çıktı. Örneklerin bir kısmında literatürle uyumlu olarak etken mikroorganizma saptanamadı. Daha geniş kapsamlı ve kantitatif moleküler metotlar kullanılarak yapılacak olan çalışmalar üretritlerde mevcut yöntemlerle saptanamayan etkenlere ışık tutacaktır.

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Anahtar Sözcükler: Üretrit, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, cinsel yolla bulaşan hastalıklar, *Ureaplasma parvum*

INTRODUCTION

Urethritis is the most common treatable sexually transmitted disease (STD) in men. It is often associated with various etiological agents, including *Neisseria gonorrhoeae* (*N. gonorrhoeae*), *Chlamydia trachomatis* (*C. trachomatis*), *Mycoplasma genitalium* (*M. genitalium*), *Ureaplasma urealyticum* (*U. urealyticum*), *Trichomonas vaginalis* (*T. vaginalis*), *Gardnerella vaginalis* (*G. vaginalis*), herpes simplex virus (HSV), and adenovirus. Depending on the presence or absence of *N. gonorrhoeae*, urethritis can be classically categorized as gonococcal or nongonococcal. The clinical presentation of urethritis in men is characterized by urethral discharge, dysuria, meatal pruritus, and urethral irritation and is confirmed by the presence of a responsible pathogen. Beyond the acute impact of the infection itself, untreated male urethritis has serious consequences related to reproductive and sexual function and may facilitate the transmission of other STD, especially human immunodeficiency virus (1). The prevalence of STDs varies geographically, and according to WHO global estimates for 2016, there were approximately 376 million new cases of curable STDs. However, it is difficult to establish the real global burden of urethritis because of the limitations in reporting and diagnostic capability in different parts of the world (2). Routine laboratory diagnosis of urethritis depends on direct microscopy, culturing, antigen detection, and serology for antibody detection. However, many of these tests lack sensitivity specificity and do not cover multiple microorganisms in the same assay. Considering that many cases are polymicrobial, modern molecular diagnostic approaches such as multiplex polymerase chain reaction (PCR), which allow the coverage of multiple pathogens in one sample within the same analysis, have led to a significant increase in diagnostic sensitivity (3-5).

To the best of our knowledge, no data exist regarding the etiology and epidemiology of male urethritis in Cyprus. Therefore, in this study, we assessed the prevalence of microorganisms, including *N. gonorrhoeae*, *C. trachomatis*, *Mycoplasma hominis* (*M. hominis*), *M. genitalium*, *U. urealyticum*, *Ureaplasma parvum* (*U. parvum*), and *T. vaginalis*, using multiplex PCR in urethral swab samples of sexually active men who sought care for urologic examination at a university hospital in Cyprus.

MATERIALS AND METHODS

A retrospective study was conducted among 138 patients admitted to a tertiary care center in Cyprus from 2017 to 2021. Multiplex PCR test results of sexually active male patients with ≥ 5 polymorphonuclear leukocytes per high-power field on a Gram-stain of urethral secretion plus clinical symptoms suggestive of urethritis or a history of a sexual partner with STD were analyzed. In addition, patients were assessed based on age, nationality, sexual life, symptoms (urethral discharge, urethral pruritus, dysuria, irritation), history of STD, and presence of unprotected sex with an unknown partner. Only samples taken at the first admission of the patients were examined; men with positive

urine culture and post-treatment controls were excluded. The Ethics Committee of the University of Kyrenia approved the study (approval number: GÜ/ETK-22.06, date: 11.04.2022).

Swab sets for nucleic acid amplification tests (eNAT, Copan SpA, Italy) were used for sample collection. Samples were obtained by inserting swabs 1 cm into the urethra and twisting the urethra clockwise and counterclockwise three times. The swab was then placed into the tube and transferred to the medical genetics laboratory for a nucleic acid amplification test. The fast-track diagnostic urethritis plus real-time PCR kit determining *T. vaginalis*, *N. gonorrhoea*, *C. trachomatis*, *U. urealyticum*, *U. parvum*, *M. genitalium*, and *M. hominis*. were used for analysis. Qiagen Rotor-gene Q was used for DNA amplification reactions.

Statistical Analysis

Statistical analyses were performed using the SPSS software package for Windows (release 17.0.0, SPSS Inc., Chicago, Ill, USA). Descriptive statistics are given as mean (standard deviation), median, and range. Categorical variables are expressed as numbers or percentages. Chi square (χ^2) test was used to compare categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred and thirty-eight men were included in this study. The mean age of the subjects was 32.52 ± 9.51 years, 60.1% being native. The clinical and demographic features of the patients are shown in Table 1. The majority of the study group consisted of men with multiple sexual partners (65.2%), and 34 men (24.6%) had a history of urethritis. Furthermore, 93 (67.4%) of 138 men mentioned a recent history of unprotected sexual intercourse. In addition, 80.4% of the patients were symptomatic at presentation; dysuria and urethral irritation were the most common symptoms (37.2% and 36.2%, respectively).

Men with positive PCR test results were significantly more likely to describe symptoms than asymptomatic men ($p = 0.004$). Regarding sexual partners and behaviors, PCR-positive patients were more likely than other men to report multiple sexual partners and a recent history of unprotected sexual intercourse ($p = 0.027$, $p = 0.003$,

Table 1. Selected characteristics of 138 men with urethritis

	n (%)
Native	83 (60.1)
History of urethritis	34 (24.6)
Multiple sexual partners	90 (65.2)
Unprotected sexual intercourse	93 (67.4)
Symptomatic at presentation	111 (80.4)
Dysuria	52 (37.2)
Urethral irritation	50 (36.2)
Urethral discharge on examination	47 (34.1)
Meatal pruritus	33 (23.9)

respectively). Pathogen detection was significantly higher in men with a prior history of STD than in the others ($p=0.001$). The positive PCR test result was not associated with ethnicity ($p=0.272$).

At least one microorganism was identified in 59,4% of the men, with *U. urealyticum* as the most frequent pathogen (26.8%), followed by *C. trachomatis* (13%) and *M. hominis* (10.9%). None of the patients tested positive for *T. vaginalis*. More than one microorganism was identified in 25 (18.1%) samples. The distribution of the detected pathogens is shown in Table 2.

Symptomatic patients have been treated empirically with a single dose of cefixime 800 mg and doxycycline 100 mg BID. In addition, 8.7% of the patients received second-line treatment because of recurrent infection after the first-line treatment. Antibiotic regimens were adopted from the latest European Association of Urology guidelines on urinary infections (6). None of the patients had an allergic or adverse reaction to the antibiotic regimens.

DISCUSSION

This article summarizes information on the etiologic agents of male urethritis in Cyprus to encourage additional studies and better STD control.

The molecular analysis in our study revealed at least one pathogen in 59.4% of the screened patients. However, a significant number of men (40.6%) remained undetected for microorganisms. A group within acute urethritis, classified as non-specific or idiopathic urethritis, which stands for a clinical condition where no microorganisms were detected, was reported to be 20-30% in epidemiological investigations (7). Urethral inflammation that develops due to alcohol intake and local chemical irritants such as vaginal spermicides can be assessed within this group. However, the conflicting data about the prevalence of idiopathic urethritis between our study and the literature can be partly explained by the limited capacity of the PCR kit used as it cannot detect *Haemophilus* species, HSV, *Adenovirus*, and *G. vaginalis*, which are also discussed to be the causes of urethritis with prevalences of around 12%, 4%, 4% and 14% respectively (8-11).

Our study demonstrated *U. urealyticum* as the most frequent pathogen responsible for male urethritis, followed by *C. trachomatis* with prevalences of 26.8% and 13%, respectively. This result contradicts the current literature as *C. trachomatis* is the most common cause of urethritis and accounts for 20-50% of all NGU

cases (12,13). However, local distributions of the pathogens may vary geographically, which may be the reason for our discordant findings. Additionally, *U. urealyticum* was the most frequent pathogen found in vaginal swabs of sexually active women in another paper from Cyprus (14). Although *C. trachomatis* is an absolute STD pathogen, *U. urealyticum* can commensally exist in the urethra, and its pathogenic role in male urethritis is more significant in higher microbial loads. The prevalence of *U. urealyticum* in urethritis is 5-26% in the literature. In two recent investigations by Sarier et al. (15), the prevalence of *U. urealyticum* was 27,1% using a non-quantitative PCR assay and 9.5% using a quantitative PCR assay (16). Although the prevalence of STDs varies geographically, a qualitative PCR test conducted in our study may also explain the difference between the literature and the current study.

Of 138 men, 10.9% and 10.1% were infected by *M. hominis* and *U. parvum*. In contrast to *U. urealyticum* and *M. genitalium*, there is little evidence for *U. parvum* and *M. hominis* to be considered causes of urethritis as they both exist in the urethra commensally (5). *U. parvum* and *M. genitalium* were found as co-infection forms in the current study, and this finding may suggest that they are secondary causes of infection due to damaged flora. Additionally, publications suggest that both microorganisms can be considered causes of urethral inflammation under high microbial loads (17). Therefore, we believe that future analyses with quantitative PCR will play an essential role in the diagnosis as it allows the detection of microbial load.

The overall prevalence of gonococcal infection in this study was 9.4%. It is estimated that NG causes 5%-20% of male urethritis cases in the United States (18). However, higher prevalences from Japan (30%) and Bangladesh (30.27%) have also been reported (3,9). The prevalence of STDs varies significantly among countries, and this may explain the variation in prevalence between our study and other reports (19).

The prevalence of polymicrobial infection in our study was 18.1%, which agrees with previous studies (16.7%) (20). It is a well-known fact that multiple microorganisms can be associated with acute urethritis (5). Therefore, setting up a diagnosis of urethral inflammation and starting the treatment depending only on conventional laboratory tests may fail in case of an existing co-infection. Previous studies have controversies in the classification of acute urethritis, discussing whether commensal microorganisms in the urethral flora can be considered actual pathogens or not. This question regarding the interpretation of the detection of facultative pathogenic microorganisms arises with non-quantitative multiplex PCR assays, which is one of the main limitations of our study.

T. vaginalis is the most prevalent non-viral STD pathogen, accounting for up to 2-13% of the cases (5,21). Interestingly, none of the patients tested positive for *T. vaginalis* infection in the current study. Many reasons may explain this. First, *T. vaginalis* infection of the male genitourinary tract is generally asymptomatic and self-terminating nature. In addition, studies suggest that the male partners of women positive for *T. vaginalis* are being treated simultaneously without any confirmatory tests (21).

Study Limitations

The main limitations of our study are the low sample size and use of a non-quantitative PCR assay with relatively limited coverage,

Table 2. Distribution of the detected pathogens

	n (%)
Positive RT-PCR	82 (59.4)
Multiple agent	25 (18.1)
<i>U. urealyticum</i>	37 (26.8)
<i>C. trachomatis</i>	18 (13)
<i>M. hominis</i>	15 (10.9)
<i>U. parvum</i>	14 (10.1)
<i>M. genitalium</i>	14 (10.1)
<i>N. gonorrhoea</i>	13 (9.4)
<i>T. vaginalis</i>	0 (0)

RT-PCR: Real-time polymerase chain reaction.

allowing only 7 of the microorganisms associated with male urethritis. Therefore, the results should be interpreted with caution, and future studies should include the detection of other possible microorganisms.

CONCLUSION

Urethritis is one of the most common STDs among men. Despite its potential influence on public health, the microbiological etiologies and pathogenic roles of each microorganism responsible for urethritis are poorly understood (9). Considering that many cases are polymicrobial and the pathogenic roles of commensal microorganisms are uncertain, future studies should focus on developing quantitative molecular diagnostic methods with determined cycle threshold values and greater microorganism coverage.

Ethics

Ethics Committee Approval: The Ethics Committee of the University of Kyrenia approved the study (approval number: GÜ/ETK-22.06, date: 11.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E., E.Ü.E., Ç.V.Ö., Concept: H.E., E.Ü.E., Ç.V.Ö., Design: H.E., E.Ü.E., Ç.V.Ö., Data Collection or Processing: H.E., E.Ü.E., Ç.V.Ö., Analysis or Interpretation: H.E., E.Ü.E., Ç.V.Ö., Literature Search: H.E., E.Ü.E., Ç.V.Ö., Writing: H.E., E.Ü.E., Ç.V.Ö.

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REFERENCES

- Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases: 2-volume set: Elsevier Health Sciences 2014.
- Organization WH. Report on global sexually transmitted infection surveillance 2018. 2018.
- Jahan F, Shamsuzzaman SM, Akter S. Diagnosis of common bacterial causes of urethritis in men by Gram stain, culture and multiplex PCR. *Malays J Pathol* 2014; 36: 175-80
- Kriesel JD, Bhatia AS, Barrus C, Vaughn M, Gardner J, Crisp RJ. Multiplex PCR testing for nine different sexually transmitted infections. *Int J STD AIDS* 2016; 27: 1275-82.
- Sarier M, Kukul E. Classification of non-gonococcal urethritis: a review. *Int Urol Nephrol* 2019; 51: 901-7.
- Schneede P, Hofstetter AG, Naber KG, Vahlensieck W, Ludwig M, Bach D, et al. [European Association of Urology guidelines on urinary and male genital tract infections]. *Urologe A* 2003; 42: 104-12.
- Bowie WR, Alexander ER, Stimson JB, Floyd JF, Holmes KK. Therapy for nongonococcal urethritis: double-blind randomized comparison of two doses and two durations of minocycline. *Ann Intern Med* 1981; 95: 306-11.
- Bradshaw CS, Tabrizi SN, Read TR, Garland SM, Hopkins CA, Moss LM, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. *J Infect Dis* 2006; 193: 336-45.
- Ito S, Hanaoka N, Shimuta K, Seike K, Tsuchiya T, Yasuda M, et al. Male non-gonococcal urethritis: From microbiological etiologies to demographic and clinical features. *Int J Urol* 2016; 23: 325-31.
- Deza G, Martin-Ezquerro G, Gómez J, Villar-García J, Supervia A, Pujol RM. Isolation of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in urethral exudates from men with acute urethritis: a descriptive study of 52 cases. *Sex Transm Infect* 2016; 92: 29-31.
- Shigehara K, Kawaguchi S, Sasagawa T, Furubayashi K, Shimamura M, Maeda Y, et al. Prevalence of genital *Mycoplasma*, *Ureaplasma*, *Gardnerella*, and human papillomavirus in Japanese men with urethritis, and risk factors for detection of urethral human papillomavirus infection. *J Infect Chemother*. 2011; 17: 487-92.
- Ito S, Yasuda M, Kondo H, Yamada Y, Nakane K, Mizutani K, et al. Clinical courses of herpes simplex virus-induced urethritis in men. *J Infect Chemother* 2017; 23: 717-9.
- Kurahashi T, Miyake H, Nakano Y, Shinozaki M, Oka N, Tanaka K, et al. A comparison of clinical features between chlamydial and non-chlamydial urethritis in men negative for gonococcal infection who attended a urological outpatient clinic in Japan. *Int Urol Nephrol* 2007; 39: 809-13.
- Zimmermann R, Cumanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. *Eur Urol* 2009; 56: 418-24.
- Sarier M, Demir M, Goktas S, Duman I, Buyukkinaci M, Yuksel Y, Tekin S, Yavuz AH, Sengul A. Results of Real-time Multiplex Polymerase Chain Reaction Assay in Renal Transplant Recipients With Sterile Pyuria. *Transplant Proc* 2017; 49: 1307-11.
- Sarier M, Sepin N, Duman I, Demir M, Hizel A, Göktepe Ş, et al. Microscopy of Gram-stained urethral smear in the diagnosis of urethritis: Which threshold value should be selected? *Andrologia* 2018; 50: e13143.
- Cox C, McKenna JP, Watt AP, Coyle PV. *Mycoplasma parvum* and *Mycoplasma genitalium* are found to be significantly associated with microscopy-confirmed urethritis in a routine genitourinary medicine setting. *Int J STD AIDS* 2016; 27: 861-7.
- Bachmann LH, Manhart LE, Martin DH, Seña AC, Dimitrakoff J, Jensen JS, et al. Advances in the Understanding and Treatment of Male Urethritis. *Clin Infect Dis* 2015; 61 Suppl 8: S763-9.
- Hailemariam M, Abebe T, Mihret A, Lambiyi T. Prevalence of *Neisseria gonorrhoea* and their antimicrobial susceptibility patterns among symptomatic women attending gynecology outpatient department in Hawassa referral hospital, Hawassa, Ethiopia. *Ethiop J Health Sci* 2013; 23: 10-8.
- Huang C, Zhu HL, Xu KR, Wang SY, Fan LQ, Zhu WB. *Mycoplasma* and *ureaplasma* infection and male infertility: a systematic review and meta-analysis. *Andrology* 2015; 3: 809-16.
- Edwards T, Burke P, Smalley H, Hobbs G. *Trichomonas vaginalis*: Clinical relevance, pathogenicity and diagnosis. *Crit Rev Microbiol* 2016; 42: 406-17.