



# The Evaluation of Urethritis in Men Caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*: Ten-year Retrospective Data from Turkey

*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum* ve *Mycoplasma hominis*'in Etken Olduğu Erkek Üretrit Olgularının Değerlendirilmesi: Türkiye'den On Yıllık Retrospektif Veri

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## ABSTRACT

**Objective:** Sexually transmitted diseases are one of the most important health issues that cause economic and social problems. Urethritis is one of the most common clinical manifestations. Patients who are especially asymptotically infected with resistant microorganisms continue to infect others; thus, surveillance is important. Our study retrospectively evaluated urethritis cases in males over 10 years for causative agents and their antibiotic susceptibilities.

**Methods:** This study included 748 male patients with urethritis. Urethral discharge swab and ejaculation samples were examined for isolation and antibiotic susceptibilities of *N. gonorrhoeae* (Biomerieux, France), *M. hominis*, and *U. urealyticum* (Mycoplasma IES, Autobio). Additionally, rapid chromatographic immunoassay (Ultimed) was used for *C. trachomatis* antigen detection.

**Results:** Of 748 patients, 166 (22.2%) were positive for at least one microorganism, whereas 28 showed a mixed infection. The most prevalent microorganism was *U. urealyticum* (114 patients, 58.8%), followed by *N. gonorrhoeae* (43 patients, 21.6%), *M. hominis* (24 patients, 12.4%), and *C. trachomatis* (10 patients, 5.2%). Most of the *N. gonorrhoeae* strains were susceptible (92.3-100%) to cefuroxime,

## ÖZ

**Amaç:** Cinsel temasla bulaşan hastalıklar (CTBH), ekonomik ve sosyal problemlere yol açan en önemli halk sağlığı sorunlarından biridir. Üretrit en sık karşılaşılan CTBH'lerden biridir. Bu nedenle, dirençli mikroorganizmalarla özellikle asemptomatik olarak infekte kişiler enfeksiyonlarını diğer kişilere de bulaştırmaya devam edeceğinden bu etkenlerin izlenmesi çok önemlidir. Çalışmamızda 10 yıllık dönemde üretritli erkek hastalardaki etkenler ve antibiyotiklere duyarlılıkları retrospektif olarak değerlendirilmiştir.

**Yöntemler:** Yedi yüz kırk sekiz üretritli erkek hasta çalışmaya dahil edilmiştir. Üretral akıntı ve ejakülat sıvısı örneklerinde *N. gonorrhoeae* (Biomerieux, Fransa), *M. hominis* ile *U. urealyticum* (Mycoplasma IES, Autobio) varlığı ve antibiyotiklere duyarlılıkları araştırılmıştır. Ayrıca *C. trachomatis* (Ultimed) antijeni varlığı da hızlı kromatografik yöntem ile araştırılmıştır.

**Bulgular:** Yedi yüz kırk sekiz hastanın 166'sının (%22,2) incelenen etkenlerin en az biri ile infekte olduğu bulunmuş; hastaların 28'inde mikst enfeksiyon saptanmıştır. En sık saptanan etken *U. urealyticum* (114 olgu-%58,8) olmuştur; *N. gonorrhoeae* (43 olgu-%21,6), *M. hominis* (24 olgu-%12,4) ve *C. trachomatis* (10 olgu-%5,2) onu izlemiştir. *N. gonorrhoeae* suşları genellikle sefuroksim, seftriakson,

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ceftriaxone, penicillin, levofloxacin, ciprofloxacin, and tetracycline. The great majority of *U. urealyticum* strains were resistant to clindamycin (89.6%) and ciprofloxacin (78.5%). *M. hominis* strains were resistant to erythromycin (100%), clarithromycin (90%), clindamycin (70%), and ciprofloxacin (43.8%).

**Conclusion:** This study revealed that these microorganisms and their antibiotic resistance patterns remain a major public health concern for the last decade.

**Keywords:** Urethritis, *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, *U. urealyticum*, antibiotic resistance

penisilin, levofloksasin, siprofloksasin ve tetrasikline duyarlı bulunmuştur. (%92,3-100). *U. urealyticum* suşlarının büyük bir çoğunluğu klindamisin (%89,6) ve siprofloksasine (%78,5) dirençli bulunmuştur. Bunlara ilave olarak *M. hominis* suşları eritromisin (%100), klaritromisin (%90), klindamisin (%70) ve siprofloksasine (%43,8) dirençli bulunmuştur.

**Sonuç:** Sonuçlar, geçtiğimiz on yılda da etkenlerin ve antibiyotik direnç modellerinin hala önemli bir halk sağlığı sorunu olduğunu göstermiştir.

**Anahtar Sözcükler:** Üretrit, *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, *U. urealyticum*, antibiyotik direnci

## Introduction

Urethritis is one of the most common sexually transmitted diseases (STDs) that is also defined as urethral inflammation (1-4). Some common clinical signs, such as stinging or itching mucoid, mucopurulent, and/or purulent discharge, dysuria and penile irritation, and urethritis can often be asymptomatic. Urethritis may occur due to infectious or non-infectious causes, such as using condoms or spermicide and mechanical traumas (1,2,4).

*N. gonorrhoeae* is the agent of gonococcal urethritis (GU), which is still the most important agent in developing countries, whereas *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma* species, *Trichomonas vaginalis*, *Herpes simplex virus*, and Adenoviruses are the causes of non-GU (NGU) in developed countries. More commonly microorganisms than *N. gonorrhoeae* are detected (1,3-6).

Penicillins, tetracyclines, fluoroquinolones, and oral third-generation cephalosporins are recommended for *N. gonorrhoeae* therapy (7-10). Macrolides, tetracyclines, and quinolones are antibiotics of choice for the treatment of *Chlamydia*, *Mycoplasma*, and *Ureaplasma* due to the emergence of resistance, and antibiotic susceptibilities should also be tested (11,12).

This study aimed to report the distribution of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis* and the antibiotic resistance rates in clinical specimens obtained from male patients with urethritis in a third-step hospital between 2010 and 2019.

## Method

### Patient Population and Study Design

Between 2010 and 2019, 748 male patients with urethritis having clinical complaints and admitted to İstanbul Yeni Yüzyıl University, Medical Faculty Gaziosmanpaşa Hospital were evaluated. Male patients were 20-74 (mean; 38) years old. Patients had clinical signs, such as urethral discharge and/or dysuria. Urethral discharge, swab, and ejaculation samples were collected after the clinical examination using sterilized cotton swabs and placed in transport agar (SEEDSWAB YNo2, Eiken Chemical Co. Ltd. Tokyo, Japan). All samples were dyed with

Gram's stain and all preparations were examined for the presence of polymorph nuclear leukocytes and microorganisms.

*N. gonorrhoeae*, *M. hominis*, and *U. urealyticum* were isolated and their antibiotic susceptibilities were also tested. The antibiotic testing panels are changed in diagnostic kits over 10 years; thus, not all isolated strains could be tested for the same groups of antibiotics. The immune chromatographic method was used to detect *C. trachomatis* antigen.

### Isolation of *N. gonorrhoeae* and Antibiotic Susceptibility Testing

All samples were cultivated on the Thayer-Martine agar and incubated for 24-48 h at 35 °C in 5% CO<sub>2</sub> atmospheric conditions to isolate *N. gonorrhoeae*. The identification was performed using VITEK-2. The antimicrobial susceptibility testing was performed by disc diffusion method for cefuroxime, ceftriaxone, penicillin, levofloxacin, ciprofloxacin, and tetracycline according to the recommendations of Centers for Disease Control and Prevention (2005) and Clinical & Laboratory Standards Institute (2012) (13,14). During the antimicrobial susceptibility testing, our results were confirmed with the results of clinical *N. gonorrhoeae* strains that were performed in an accredited laboratory to validate the internal quality of our test conditions.

### Isolation of *M. hominis* and *U. urealyticum* and Antibiotic Susceptibility Testing

A quantitative commercial test (Mycoplasma IES, Autobio) was used to identify and test the antibiotic susceptibility (roxithromycin, clarithromycin, erythromycin, ofloxacin, tetracycline, ciprofloxacin, clindamycin, and levofloxacin) of *M. hominis* and *U. urealyticum*. This test detects urease and arginase activities by releasing NH<sub>3</sub> to identify *Ureaplasma* and *Mycoplasma*, respectively. The positive results were determined with color changes in the wells that contain antibiotics, wherein changes mean that the bacterium is resistant. The tests were performed following the manufacturer's recommendations.

### Detection of *C. trachomatis* Antigen

A rapid chromatographic immunoassay (Ultimed) was used to detect *C. trachomatis* antigen. The test was performed according to the manufacturer's recommendations.

## Results

### Distributions of Patients, Clinical Samples, and Detected Microorganisms

A total of 987 patients with prediagnosed urethritis were evaluated. To determine the prevalence and antibiotic resistance rates of causative microorganisms, 748 (75.8%) male patients were included in the present study, wherein 165 (22.05%) were positive for at least one investigated microorganism. Among 165 patients with urethritis, 28 (16.9%) have mixed infection (infected with more than one causative agent). A total of 194 different microorganisms were detected. Except for one urine and three ejaculate samples, the majority of the clinical samples were urethral swabs.

The distributions of positive patients for urethritis according to years were shown in Table 1; in years 2015 and 2017 the positivity was the highest. In 2011, only eight patients were found to be infected with the investigated microorganisms.

*U. urealyticum* (114 patients) was revealed as the most prevalent microorganism over a 10-year period, which was followed by *N. gonorrhoeae* (43 patients), *M. hominis* (24 patients), and *C. trachomatis* (10 patients) (Figure 1).

### Antibiotic Susceptibility Results

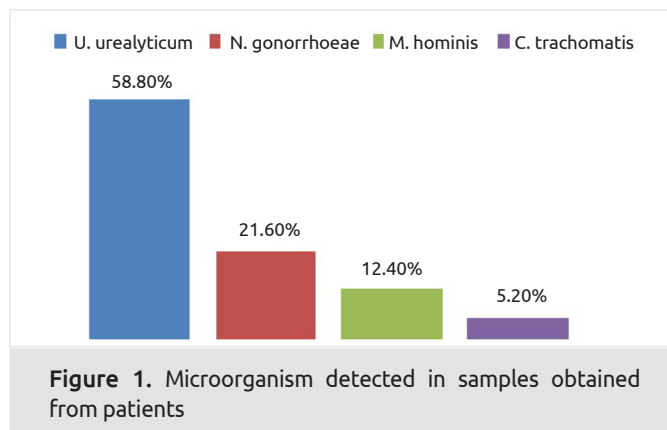
All 42 *N. gonorrhoeae* strains isolated over the 10-year period were susceptible (92.3-100%) to all six tested antibiotics (Table 2).

The resistance rate of *U. urealyticum* strains to clindamycin was 89.6%, followed by ciprofloxacin (78.5%) and tetracycline (43.9%). Strains were also intermediate resistant to ofloxacin (47.5%) (Table 3).

All *M. hominis* strains were resistant to erythromycin, followed by clarithromycin (90%), clindamycin (70%), and ciprofloxacin (43.8%) (Table 4).

## Discussion

Urethritis is the most common syndrome among STDs, which are globally important public health concerns (3,5,15,16). Early



diagnosis and treatment were implicated. Increasing resistance rates in agents of STDs is also very important and can cause treatment failure (3,17,18).

*N. gonorrhoeae* and *C. trachomatis* remain as the most important causative agents of urethritis in male patients (2,4,5,8). Asymptomatic cases are frequent and important for infection transmission (19-21). The body of evidence suggests that *N. gonorrhoeae* has a great capacity to develop antibiotic resistance, and in many countries, resistance rates are very high to penicillin, macrolides, tetracycline, and quinolones; therefore, ceftriaxone (extended-spectrum cephalosporin) has become an important antibiotic (17,18,22). The World Health Organization and CDC have emphasized the importance of surveillance studies performed by culture and antibiotic susceptibility testing to prevent the dissemination of multidrug-resistant *N. gonorrhoeae* strains (18).

Previous studies from India, Kuwait, Zimbabwe, and the United States reported that the detection rates of *N. gonorrhoeae* and *C. trachomatis* from male patients range 23.9-81.9% and 12.4-31.4%, respectively according to different geographical regions (17,23-25).

A study reported from France analyzed 1,944 cases of urethritis in male patients during 10 years and 38% of patients were found

**Table 1.** Distributions of the detected microorganisms from clinical samples in 10 years

Years	Number of patients	Number of microorganisms detected from the patients			
		<i>U. urealyticum</i>	<i>N. gonorrhoeae</i>	<i>M. hominis</i>	<i>C. trachomatis</i>
2010	14	12	2	5	0
2011	8	5	4	2	0
2012	14	10	4	2	0
2013	15	10	4	4	0
2014	13	9	4	1	0
2015	34	23	14	4	0
2016	20	11	4	1	5
2017	22	11	6	3	4
2018	9	9	0	0	1
2019	16	14	1	2	0

**Table 2. Antibiotic susceptibilities of *N. gonorrhoeae* strains**

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)
CRO	36	100	0
CXM	36	100	0
P	30	93.3	6.6
LEV	29	93.1	6.9
CIP	36	91.6	8.3
TET	26	92.3	7.7

CXM: Cefuroxime, CRO: Ceftriaxone, P: Penicillin, LEV: levofloxacin, CIP: Ciprofloxacin, TET: Tetracycline

**Table 3. Antibiotic susceptibilities of *U. urealyticum* strains**

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)	Intermediate (%)
ROX	95	85.3	6.3	8.4
E	81	90.1	9.8	0
CLAR	80	83.6	11.3	5
CLIN	77	6.5	89.6	3.9
CIP	107	9.3	78.5	12.1
OFX	101	23.7	28.7	47.5
LEV	78	78.2	11.5	10.3
TET	82	36.6	43.9	19.5

ROX: Roxithromycin, CLAR: Clarithromycin, E: Erythromycin, OFX: Ofloxacin, TET: Tetracycline, CIP: Ciprofloxacin, CLIN: Clindamycin, LEV: Levofloxacin

to be infected with *C. trachomatis* while the isolation rate of *N. gonorrhoeae* was 32.5%. Additionally, 6.7% of the patients were found to be co-infected (5). Our study also includes strains that are isolated from the samples obtained in male patients in the last 10 years. Our isolation rates were 21.6% and 5.2% for *N. gonorrhoeae* and *C. trachomatis*, respectively, and the difference between isolation rates can be associated with the number of included patients and techniques used to detect microorganisms.

Many literature reports on antibiotic susceptibility were also investigated. As an example, Hamasuna et al. (26) reported that the majority of *N. gonorrhoeae* strains were resistant to ciprofloxacin in Japan. The prevalence of fluoroquinolone resistance rates of *N. gonorrhoeae* has been reported to reach almost 70% (26-28).

A study by Buder et al. (18) in Germany revealed that a total of 537 *N. gonorrhoeae* strains were isolated during an extended surveillance program in the whole country, wherein none of the strains were found to be resistant to ceftriaxone but with resistance rates to azithromycin and ciprofloxacin of 10.8% and 64.9%, respectively. Consistent with Buder et al. (18), Latif et al. (17) reported that all *N. gonorrhoeae* strains were susceptible to ceftriaxone and cefixime, but resistance to ciprofloxacin and kanamycin were 18.6% and 2%, respectively. Contrarily, many literatures reported the susceptibility rates of *N. gonorrhoeae* strains showed to be decreased to cefixime (29,30).

Yeshanew and Geremew (15) found in Ethiopia that, among

**Table 4. Antibiotic susceptibilities of *M. hominis* strains.**

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)	Intermediate (%)
ROX	14	71.4	14.2	14.2
E	10	0	100	0
CLAR	10	10	90	0
CLIN	10	30	70	0
CIP	16	37.5	43.8	18.8
OFX	14	78.6	7.1	14.3
LEV	10	80	10	10
TET	10	90	0	10

ROX: Roxithromycin, CLAR: Clarithromycin, E: Erythromycin, OFX: Ofloxacin, TET: Tetracycline, CIP: Ciprofloxacin, CLIN: Clindamycin, LEV: Levofloxacin

207,044 gonorrhoeae suspected patients, 20.8% were confirmed to be infected with *N. gonorrhoeae*. All isolated strains were resistant to tetracycline (100%) and penicillin (100%), and resistance rates to ciprofloxacin, ceftriaxone, and cefoxitin were 52%, 48%, and 44%, respectively (15).

Some studies revealed that *N. gonorrhoeae* strains are found resistant to various antibiotics, even to ceftriaxone (15,26-28); however, in our study, none of the strains were resistant to ceftriaxone and cefuroxime and even penicillin-resistance rates were found to be low (6.6%).

In Turkey, Balıkcı and Aydın (31) reported that 1,226 *N. gonorrhoeae* strains were found to be susceptible to ceftriaxone, cefuroxime, and cefoxitin. However, resistance rates of penicillin, tetracycline, and ciprofloxacin were 62%, 61%, and 33%, respectively (31). Another study from Turkey revealed that, among 78 *N. gonorrhoeae* strains, the resistance rate was 64% for penicillin and 75.7% for tetracycline, whereas doxycycline, azithromycin, and ciprofloxacin were found to be the most effective antibiotics (22). In the present study, resistance rates to penicillin (6.6%), tetracycline (7.7%), and ciprofloxacin (8.3%) were much lower as mentioned above.

*U. urealyticum* and *M. hominis* is well known to colonize the genital tract when people were born, colonization rates increase up to 60% of the population after puberty, and that they can be responsible for some clinical manifestations, such as NGU, cervicitis, and cystitis (20,32). Generally, the prevalence of *U. urealyticum* in patients with NGU is nearly 6-60%, and infections are associated with socioeconomic status and education levels of the population (17,31).

Authors from Switzerland, China, Cuba, Africa, and Serbia informed that isolation rates of *Ureaplasma* and *Mycoplasma* from patients with urethritis range 13-89% according to different geographical regions (34-38).

Various reports from Turkey showed that isolation rates of *U. urealyticum* and *M. hominis* reached up to 82% and 30%, respectively (33). Pelit et al. (16) reported that *U. urealyticum* was the most prevalent (32%) microorganism that is isolated from the



urethral discharges of 140 male patients followed by *M. hominis* (10.7%), *C. trachomatis* (8.6%), and *N. gonorrhoeae* (8.6%). Our study revealed that the isolation rate of *U. urealyticum* (58.8%) was higher than *N. gonorrhoeae* (21.6%), thus our results appear to support previous studies.

Quinolone resistance of *Ureaplasma* (0-62.5%) and *Mycoplasma* (17.6-41.2%) strains is increasing (32,39-41). Resistance rates of *Mycoplasma* and *Ureaplasma* strains to doxycycline, roxithromycin, and tetracycline were reported as 0-8%, 0-30%, and 19-50%, respectively. Thus doxycycline, clarithromycin, and azithromycin are most recommended antibiotics (42).

Our results revealed that resistance rates of *U. urealyticum* strains to clindamycin, quinolones, and tetracycline were 89.6%, 47.5-78.5%, and 43.9%, respectively. Additionally, *Ureaplasma* strains were susceptible to erythromycin (90.1%), roxithromycin (85.3%), and clarithromycin (83.6%). Similar to *U. urealyticum*, resistance rates of *M. hominis* strains were high to clindamycin (70%) and ciprofloxacin (43.8%). Tetracycline was also effective to *Mycoplasma* strains (90%) but not to *Ureaplasma* strains (36.6%). Therefore, roxithromycin was the most effective antibiotic against both *Ureaplasma* and *Mycoplasma* strains, with resistance rates of 14.7% and 28.6%, respectively.

## Study Limitations

Limitations of our study include insufficient demographical data, knowledge about recent antibiotic usage and serological test results (anti-HIV, anti-syphilis, etc.), and the number of sexual partners or unprotected sexual intercourse. We also failed to perform antibiotic susceptibility testing for *C. trachomatis*.

Additionally, our training hospital is a third-step hospital, and patients are mostly admitted after a prior antibiotic therapy and due to financial difficulties, all diagnostic procedures could not be performed to clearly define urethritis etiology. Therefore, our number of positive cases, such as *N. gonorrhoeae*, is lower than some of the reported studies. The low prevalence rates could be the reason for lower resistance rates compared with previous studies.

## Conclusion

Our results proved that, among the four major STD agents, *U. urealyticum* was the most common for the last decade in symptomatic male patients with urethritis. Roxithromycin is found to be the most effective antibiotic for both *Ureaplasma* and *Mycoplasma* strains. As mentioned in previous studies, *N. gonorrhoeae* strains were susceptible to mostly used therapeutic agents.

## Ethics

**Ethics Committee Approval:** Ethical approval has been obtained from İstanbul Yeni Yüzyıl University Medical Faculty Research Ethics Committee (meeting date: 2020/04-05).

**Informed Consent:** Retrospective study.

## Authorship Contributions

Surgical and Medical Practices: D.B.T., Concept: D.B.T., Design: D.B.T., D.G., F.K.Y., Data Collection or Processing: D.B.T., D.G., F.K.Y., Analysis or Interpretation: D.G., F.K.Y., Literature Search: D.G., F.K.Y., Writing: D.G., F.K.Y.

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