

# Development of Antibiotic Resistance Against *Ureaplasma urealyticum* Strains Isolated from Urogenital Samples

## Ürogenital Örneklerden İzole Edilen *Ureaplasma urealyticum* Suşlarına Karşı Antibiyotik Direnç Gelişimi

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### What's known on the subject? and What does the study add?

In this study, resistance of *Ureaplasma urealyticum* strains isolated from urogenital samples to antibiotics in 2001, 2008 and 2013 is evaluated. Sensitivity to tetracycline and doxycycline was found to be continued at high rates. High resistance to ofloxacin and ciprofloxacin were observed.

### Abstract

**Objective:** To assess any change in the antibiotic sensitivity of *Ureaplasma urealyticum* strains isolated from urogenital samples in the course of time.

**Materials and Methods:** Hospital records were retrospectively examined and cases with growth of *U. urealyticum* in urogenital samples in the years 2008 and 2013 were identified. Furthermore, the change in the course of time was examined by taking into consideration the cases we reported in 2001.

**Results:** Higher rates of sensitivity against tetracycline and doxycycline were observed in 60 patients with isolated *U. urealyticum*. Higher rates of resistance against ofloxacin and ciprofloxacin were observed. A significant difference was found in resistance against antibiotics when the records of 2008 and 2013 were compared. A statistically significant increase was found in resistance against ofloxacin and ciprofloxacin when the records of 2001 were compared with the records of 2008 and 2013 ( $p<0.0005$ ).

**Conclusion:** *U. urealyticum* strains demonstrated high levels of resistance to quinolones. Resistance development is increasing in the course of time. Sensitivity against tetracycline and doxycycline has continued at high rates. It would be beneficial to consider these results during empirical treatment to be applied in cases ineligible for culturing.

**Keywords:** *Ureaplasma urealyticum*, Resistance to quinolones, Urethritis

### Öz

**Amaç:** Ürogenital örneklerden izole edilen *Ureaplasma urealyticum* suşlarının antibiyotiklere karşı duyarlılıklarının zaman içerisinde değişip değişmediğinin değerlendirilmesidir.

**Gereç ve Yöntem:** Hastane kayıtları retrospektif olarak incelenerek 2008 ve 2013 yılları içerisinde ürogenital örneklerde *U. urealyticum* üreyen olgular belirlenmiştir. Ayrıca 2001 yılında tebliğ ettiğimiz olgular göz önünde bulundurularak zaman içerisindeki değişim incelenmiştir.

**Bulgular:** *U. urealyticum* izole edilen 60 hastada tetrasiklin ve doksisisikline karşı yüksek oranlarda duyarlılık gözlenmiştir. Ofloksasin ve siprofloksasine karşı direncin yüksek oranlarda olduğu gözlenmiştir. 2008 ve 2013 yılları karşılaştırıldığında antibiyotiklere karşı direnç oranlarında anlamlı bir farklılık gözlenmemiştir. 2001 yılı kayıtları 2008 ve 2013 yılları kayıtları ile karşılaştırıldığında ofloksasin ve siprofloksasine karşı direncin istatistiksel olarak anlamlı bir şekilde arttığı gözlenmiştir ( $p<0,0005$ ).

**Sonuç:** *U. urealyticum* suşları kinolonlara karşı yüksek oranda direnç göstermektedirler. Zaman içerisinde direnç gelişimi artmaktadır. Tetrasiklin ve doksisisikline karşı duyarlılık yüksek oranlarda devam etmektedir. Kültür yapılamayan olgularda uygulanacak olan ampirik tedavide bu durumun göz önünde bulundurulması yararlı olacaktır.

**Anahtar Kelimeler:** *Ureaplasma urealyticum*, Kinolonlara direnç, Üretrit

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## Introduction

*Ureaplasma urealyticum* is a species belonging to the genus *Ureaplasma* and the family of *Mycoplasmataceae* in the order mycoplasmalates and class of *Mollicutes* of bacteria. Bacterial species *U. urealyticum* and *Ureaplasma parvum* under the *Ureaplasma* genus are found to be disease-causing agents in human beings (1).

This bacterium was initially recognized during the 1950's after being isolated in non-gonococcal urethritis cases (2). Later during the 1960's, it was renamed as T-*mycoplasmas* after its characteristics were better understood (3). Finally in 1974, the current name *U. urealyticum* was given on the basis of its impact on urea and other metabolic characteristics (4). Fourteen serotypes of *U. urealyticum* have been defined. Serotypes 1, 3, 6, and 14 were defined as *U. parvum* since they are responsible more likely from gynecological and neonatal infections. However, other serotypes are still named as *U. urealyticum* (5).

*U. urealyticum* causes upper respiratory tract and lower urinary tract infections in humans. Urethritis, cystitis, epididymo-orchitis, prostatitis, salpingitis and pelvic inflammatory disease are among the resulting diseases (6,7). It is also suggested to increase risk of stone formation due to its urea breakdown effect (8). It is also known to be a significant risk for adverse pregnancy outcomes and complications of preterm birth (9). It may rarely be present in intra-articular fluids.

*U. urealyticum* does not grow in routine bacterial culture media. Specific culture media are used to detect this bacterium and implement antibiotic sensitivity tests. Although techniques, such as polymerase chain reaction, are used for diagnostic purposes, such methods do not provide any information on antibiotic sensitivity.

Absence of cell wall is the main specific characteristic of this family of bacteria. Therefore, antibiotics acting by impairing cell wall synthesis are not efficacious on this group of bacteria. Tetracycline, fluoroquinolone and macrolides are among the efficacious antibiotics. Development of resistance in particular against fluoroquinolone is observed in the course of time.

This study aims at assessing antibiotic sensitivity of *U. urealyticum* and the antibiotic resistance developing in the course of time.

## Materials and Methods

This is a retrospective study. We analyzed the records of our hospital and identified the results positive for bacterium *U. urealyticum* in the samples taken from patients attended our urology unit in 2008 and 2013. The test reports were documented and examined.

*Mycoplasma* IST 2 test kit (BioMérieux, Marcy- l'Etoile, France) is used in our hospital for the diagnosis of *Mycoplasma* infections. This kit allows for both isolation of bacteria and sensitivity test against nine antibiotics.

Resistance against antibiotics was assessed, by comparing the test results obtained in 2008 and 2013 with the use of chi-square test. By this way, it was investigated whether or not there occurred any difference in antibiotic resistance within a period of five years.

## Statistical Analysis

The results of these two years were compared with the rate of antibiotic resistance of *U. urealyticum* strains isolated within the first six months of 2000, as presented in 2001, and thus, the difference in resistance within a period of 14 years was also investigated. Chi-square test was used for this assessment. Samples (10) obtained in 2001 were examined using the *Mycoplasma* IST kit (BioMérieux, Marcy- l'Etoile, France) and sensitivity to seven antibiotics was tested.

## Results

Results of 60 patients were accessible from the hospital records. 26 of these patients were tested in 2008, whereas 34 in 2013. The mean age of the patients was  $37.9 \pm 11.4$  years (21-74). Twenty-five patients were female and all samples taken were urine.

Thirty-five patients were male and *U. urealyticum* was isolated from the urine of 7 patients and ejaculate of 28 patients.

Antibiotic sensitivity of the *U. urealyticum* strains isolated in 2008 and 2013 is given in Table 1. Among the nine antibiotics tested, highest sensitivity rates were observed in tetracycline and doxycycline and highest resistance rates in ofloxacin and ciprofloxacin. Resistance to ofloxacin was found in 12%, whereas this rate was 62% for ciprofloxacin. No statistically significant difference was found in terms of the resistance rate against the nine tested antibiotics when data of 2008 and 2013 were compared ( $p > 0.5$ ).

When the antibiotic resistance rate of the strains isolated in 2001 was compared with that of the strains isolated in 2008 and 2013; the increase in resistance to ofloxacin and ciprofloxacin was observed to be statistically significant ( $p < 0.0005$ ). No statistical significant change was found in resistance against other antibiotics ( $p > 0.5$ ).

The rate of antibiotic resistance of *U. urealyticum* strains resulting from various studies are given in Table 2 (10,11,12,13,14,15,16). This table, in particular, underlines the high level of resistance to fluoroquinolones.

**Table 1. Antibiotic sensitivity for *U. urealyticum* in 2008 and 2013 n (%)**

Antibiotic	2008			2013	
	S	I	R	S	I
Tetracycline	26 (100)	0 (0)	0 (0)	34 (100)	0 (0)
Doxycycline	26 (100)	0 (0)	0 (0)	34 (100)	0 (0)
Erythromycin	22 (84)	3 (12)	1 (4)	31 (91)	0 (0)
Clarithromycin	22 (84)	2 (8)	2 (8)	30 (88)	1 (3)
Azithromycin	23 (88)	3 (12)	0 (0)	31 (91)	0 (0)
Josamycin	24 (92)	1 (4)	1 (4)	34 (100)	0 (0)
Pristinamycin	23 (88)	1 (4)	2 (8)	34 (100)	0 (0)
Ofloxacin	10 (38)	13 (50)	3 (12)	10 (29)	20 (59)
Ciprofloxacin	1 (4)	9 (34)	16 (62)	3 (9)	10 (29)

S: Sensitive, I: Intermediate, R: Resistance

**Table 2. Antibiotic resistance rates against *Ureaplasma urealyticum* as obtained in various studies (%)**

Author	n	Gender	Tet	Dox	Ery	Clair	Azt	Jos	Prs	Ofi	Cip
Saraçoğlu and Aydınli (10)	18	M	0	5.6	0	0	0	-	-	0	0
Schneider et al. (11)	140	F, M	--	--	1.9	4.9	1	--	--	9.7	19.4
Pignanelli et al. (12)	542	F	2.9	1.7	18.9	14.6	6.3	3.7	2.1	5.6	40.7
Bayraktar et al. (14)	27	F	0	0	34.7	12.5	25	0	0	81.3	84.4
Diaz et al. (13)	150	F		16	46	63				64	
Leli et al. (16)	152	M, F	--	0	0	--	0	0	0	27.6	66.4
This study	60	M, F	0	0	7	8	5	2	3	12	62

M: Male, F: Female, Tet: Tetracycline, Dox: Doxycycline, Ery: Erythromycin, Clair: Clarithromycin, Azt: Azithromycin, Jos: Josamycin, Prs: Pristinamycin, Ofi: Ofloxacin, Cip: Ciprofloxacin

## Discussion

*U. urealyticum* is a bacterium that potentially causes upper respiratory tract, lower urinary tract and genital system infections in adults. It is also known to play a role in neonatal infections. Inability of the growth of this bacterium in the routinely used culture media makes it difficult for isolation. Samples of increasing number of patients are isolated in the recent years thanks to the media, which are specially developed for the growth of this specific bacterium and are now in routine practice (10,16).

*U. urealyticum* is innately resistant to certain antibiotics given its absence of bacterial cell wall. Beta-lactam antibiotics including penicillin and cephalosporin, glycopeptides including vancomycin and teicoplanin and phosphomycin are the antibiotics inefficacious against this bacterium. Furthermore, polymyxin, sulphonamide, trimethoprim, nalidixic acid and rifampicin are also not efficacious. When the above given matters are taken into consideration, it is understood that majority of the antibiotics used in empirical treatment in daily practice have no effect on *U. urealyticum*.

The main antibiotics efficacious on *U. urealyticum* are tetracyclines, macrolides, fluoroquinolones and pristinamycin.

Although fluoroquinolones are the most commonly used antibiotics, development of resistance to these antibiotics is a major concern.

In the recent 4 years, the incidence of *U. urealyticum* has been increasing continuously. Therefore, we wonder if the antimicrobial resistance of *U. urealyticum* and *Mycoplasma hominis* has changed. The fluoroquinolone resistance rate in *Ureaplasma* spp. varies widely among different countries and studies. For instance, in a recent study carried out in Switzerland, Schneider et al. (11) reported a rate of non-susceptibility to ciprofloxacin of 19.4%, while in a recent study in Italy, 41% of isolates were ciprofloxacin-resistant (12). In our study, the rate of ciprofloxacin resistance was 62%. Diaz et al. (13) reported that less than 35% of *U. urealyticum* isolates in Cuba were resistant to minocycline, pefloxacin, doxycycline, tetracycline, clindamycin, and azithromycin. They showed that the rate of resistance to ofloxacin, clarithromycin, and erythromycin were 64.3%, 63%, and 46.1%, respectively. In a study conducted in Turkiye on pregnant women, Bayraktar et al. (14) reported that the rate of resistance of genital mycoplasmas to doxycycline, josamycin, ofloxacin, erythromycin, tetracycline, ciprofloxacin, azithromycin, clarithromycin, and pristinamycin was 0%, 0%, 81.3%, 34.4%, 0%, 84.4%, 25%, 12.5%, and 0%,

respectively, which was the report with the most similarity to our study. In their study conducted on South African pregnant women, Redelinghuys et al. (15) reported that susceptibility of *Ureaplasma* spp. to levofloxacin and moxifloxacin was 59% and 98%, respectively. They showed that mixed isolates (*Ureaplasma* spp. and *M. hominis*) were highly resistant to erythromycin (97%) and tetracycline (97%).

Antibiotic resistance of *U. urealyticum* strains isolated from the urogenital samples obtained in 2001, 2008 and 2013 were investigated in this study. High rates of sensitivity to tetracycline and doxycycline were observed to continue. Resistance to ofloxacin and ciprofloxacin was found to be at high rates. High rates of resistance or these two antibiotics were also observed in other studies in the literature as summarized in Table 2.

### Study Limitations

Due to low number of cases, patients were not sub-grouped according to gender, age and mode of sampling. It would be useful to investigate any potential difference in terms of antibiotic sensitivity among the sub-groups of gender, age groups and modes of sampling as urine, ejaculate, urethral discharge, vaginal discharge or cervical smear in larger series.

### Conclusion

It would be beneficial to consider these sensitivity rates in the treatment of patients with suspected *U. urealyticum* infection but not eligible for culturing. Our study is important in terms of demonstrating a statistically significant increase in resistance to ofloxacin and ciprofloxacin within a period of 14 years.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: M.S., Design: M.S., R. T.D., Data Collection or Processing: M.S., Analysis or Interpretation: A.E., M.S., Literature Search: R.T.D., A.E., Writing: M.S., A.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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