Prevalence of Mycoplasma/Ureaplasma Infections in Women Presenting with Recurrent Vaginitis in the Ambulatory Setting

Esra Demirel, M.D., Stephanie Trentacoste McNally, M.D., Weiwei Shan, Ph.D., and Gary L. Goldberg, M.D.

OBJECTIVE: To redefine recurrent vaginitis in the ambulatory setting and offer information to consider searching for additional vaginal microbes such as Mycoplasma/Ureaplasma *that could cause persistent vaginitis symptoms.*

STUDY DESIGN: This is a retrospective chart review of 3,849 office visits coded with an ICD-9 and ICD-10 code for vaginitis. Of the reviewed charts, 553 visits showed at least 1 episode of Mycoplasma *and/or* Ureaplasma *infection. Incidence, demographics, concurrence with other infections, and recurrence rates were analyzed, where recurrence was defined as return to clinic for vaginitis symptoms >2 times a year or for 2 consecutive years.*

RESULTS: The prevalence of Ureaplasma/Mycoplasma *was 14% in this ambulatory site, and 73.4% of those women returned with recurrent symptoms. There were no significant differences in the rates of recurrent vaginitis for women based on ethnicity, race, or relationship status. The differences between contraceptive categories were significantly different where most of the recurrent infections occurred in women using hormonal contraceptive measures.*

CONCLUSION: If a woman has persistent vaginitis symptoms and seeks care more than once a year or returns for continued symptoms in subsequent years, there may be additional pathogens that need to be addressed. (J Reprod Med 2021;66:3–8)

…persistent vaginitis symptoms and [need for] physical examination more than 1 time a year or returning for continued symptoms in subsequent years [suggest] there may be additional pathogens that need to be addressed.

Keywords: bacterial vaginosis, mycoplasma, ureaplasma, vaginal microbiome, vaginitis, vulvovaginitis.

According to 2016 statistics, vaginitis accounts for 7% of ambulatory gynecology visits per year.[1] The Centers for Disease Control and Prevention (CDC) estimates that 75% of women will have at least 1 episode of vulvovaginitis per year, and 40–45% will have 2 or more episodes.[2] The current CDC guidelines define recurrent vulvovaginal infections as 4 or more episodes of symptomatic infections per year. Less than 5% of women have recurrent infections. How-

From the Department of Obstetrics and Gynecology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell–North Shore University Hospital and Long Island Jewish Medical Center, Manhasset, New York.

Esra Demirel, M.D., and Stephanie Trentacoste McNally, M.D., contributed equally to this work.

Address correspondence to: Esra Demirel, M.D., Department of Obstetrics and Gynecology, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030 (edemirel@northwell.edu).

Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

0024-7758/21/6601-02–0003/$18.00/0

ever, many women do not seek treatment with a healthcare provider for symptoms of vaginitis, and the exact number of women who self-treat is unknown.[3] Therefore, the true prevalence of recurrent vaginitis is not well established.

We can track annual ambulatory and hospital visits based on symptoms and coding but lack data on all of the causative agents for each symptomatic infection. Previous research has shown a correlation between particular molliculite species and vaginal yeast and bacterial infections. In symptomatic patients, *Ureaplasma* and *Mycoplasma* have been associated with cervicitis, pelvic inflammatory disease (PID), endometritis, and infertility.[4] *Ureaplasma* is considered a part of normal genital flora, with a 40–80% colonization rate.[5] There is not a definite recommendation as to when and if to perform additional mollicute cultures in cases of vulvovaginitis. Routine screening for *Ureaplasma* and *Mycoplasma* is not currently recommended. However, for women with recurrent vaginitis even after standard CDC-recommended treatments for vaginitis, there may be value in molliculite culture to target treatment. Some research suggests it does not affect outcome and it is difficult to eradicate these infections.[6]

Previous studies have shown a broad range of molliculite coinfections with bacteria and yeast, and these molliculites range according to age and number of sexual partners.[7,8] In the current study we reassess the definition of recurrent vulvovaginitis and offer information to consider testing for *Ureaplasma* and *Mycoplasma*, which may benefit patients and treatment plans. The primary aim of this study is to establish the prevalence of *Ureaplasma* and *Mycoplasma* infections in the ambulatory setting. The secondary aim is to establish a new definition of recurrence that is more applicable to ambulatory care. With self-treatment options readily available, we also explore whether providers should consider other sources of vaginal infections for women who have more frequent office visits and have not been treated with standard medication doses. We suggest defining recurrence as women who present to the ambulatory setting with persistent symptoms of vaginitis more than 2 times in 1 year or annually for 2 consecutive years with symptoms such as discharge, pruritus, pain, or odor.

Materials and Methods

This study is a retrospective, cross-sectional study where we reviewed the electronic medical records (EMRs) in Athena Health of women who presented to a Northwell Health ambulatory office with symptomatic vaginitis. Using the EMR, 3,849 visits between 8/2013 and 12/2017 coded with an ICD-9 and ICD-10 code for vaginitis were analyzed. Of those 3,849 visits, 553 visits showed at least 1 or more episodes of confirmed *Mycoplasma* and/or *Ureaplasma* infections. Incidence, demographics, concurrence with other infections, and recurrence rates were analyzed. Recurrence was defined as return to clinic for vaginitis more than 2 times a year or 2 consecutive years.

Ureaplasma/Mycoplasma cultures were collected from vaginal secretions and transported with Affirm Vaginal Pathogens DNA Direct Probe test. All specimens were analyzed at the Northwell Health Core Lab as per their culture and reporting protocol. The ambulatory setting in which the study was carried out did not have a standardized testing protocol for *Ureaplasma/Mycoplasma* among providers. Among the 3,849 vaginitis visits that were analyzed, not all patients were routinely tested for *Mycoplasma/Ureaplasma,* and testing was up to the clinical discretion of the individual providers.

Statistical analysis was performed using RStudio 1.1.463 built on R 3.5.1 and/or SAS Studio 3.8 (Enterprise Edition) built on SAS 9.04. For patient demographics, mean and standard deviation

Table I *Demographics for the 553 Documented Cases of* Ureaplasma/Mycoplasma

	N=553	N
Mean age	29.4 (9.75)	553
Relationship status		553
Married	91 (16.5%)	
Single	460 (83.2%)	
Other	2 (0.36%)	
Ethnicity		553
Asian	15 (2.71%)	
Black/African American	102 (18.4%)	
Hispanic	72 (13.0%)	
White	305 (55.2%)	
Unknown	59 (10.7%)	
Smoking status		553
No	435 (78.7%)	
Yes	109 (19.7%)	
Unknown	9 (1.63%)	
Contraception category		553
Barrier	105 (19.0%)	
Hormonal	228 (41.2%)	
Non-hormonal	35 (6.33%)	
None	185 (33.5%)	

were reported for continuous clinical variables and frequency for categorical variables. The *t* test or Wilcoxon rank-sum test were used to compare continuous variables contingent on the normality of the variable distribution. Chi-square and Fisher's exact tests were used to compare the distribution of categorical variables between groups.

Results

Of the 3,849 documented vaginitis visits from 8/2013 to 12/2017, 553 visits showed a documented culture-confirmed *Mycoplasma* and/or *Ureaplasma* infection; therefore the prevalence of *Ureaplasma* and/or *Mycoplasma* was determined to be 14% in this ambulatory site for symptomatic patients. Of 553 culture-confirmed *Mycoplasma* and/or *Ureaplasma* cases that received treatment, 73.4% of those women (406 visits) returned with self-reported vaginitis symptoms. This was considered recurrent by our definition of 2 visits in 1 calendar year or an ambulatory visit 2 years in a row.

Recurrent cases of *Ureaplasma* and/or *Mycoplasma* were analyzed by relationship status, ethnicity, smoking status, and contraception method (Table I). When analyzed by relationship status, 83.2% of the 553 culture-confirmed cases identified as being single and 85% of the 406 recurrent cases identified as single, which was not statistically significant (p = 0.134) (Table II). By ethnicity, subjects who returned with self-reported recurrence identified as White, Black/African American, Hispanic, and Asian at 55.4%, 18.5%, 11.3%, and 1.23%, respectively (p = 0.020). The majority of the initial cohort reported being non-smokers (78.7%). The majority of the recurrent cases were also found to be non-smokers (79.3%), with no significant difference (p = 0.432).

Recurrent cases were also analyzed by contraceptive choice categorized into barrier, hormonal, non-hormonal, and none (Table II). Barrier methods included condoms. Hormonal methods included hormonal intrauterine devices (IUDs), oral contraceptive pills, patch, NuvaRing (Merck), and Nexplanon (Merck). Non-hormonal methods included copper IUD and withdrawal. The majority of the recurrent cases reported using hormonal methods (40.9%), followed by no contraceptive use (29.8%), barrier methods (21.7%), and non-hormonal methods (7.64%). The differences between contraceptive categories were significantly different (p = 0.001), where most of the recurrent infections occurred in women using hormonal contraceptive measures.

A total of 66.5% of women who returned to the office with recurrent symptoms had only a sin-

Table II *Entire Cohort of 553 Patients Stratified by Self-Reported Recurrence*

	No N = 147	Yes N = 406	p Value
Mean age	27.0 [22.5; 33.0]	26.0 [22.5; 33.0]	0.778
Relationship status			0.134
Married	31 (21.1%)	60 (14.8%)	
Single	115 (78.2%)	345 (85.0%)	
Other	1 (0.68%)	1 (0.25%)	
Ethnicity			0.020
Asian	10 (6.80%)	5 (1.23%)	
Black/African American	27 (18.4%)	75 (18.5%)	
Hispanic	17 (11.6%)	55 (13.5%)	
White	80 (54.4%)	225 (55.4%)	
Unknown	13 (8.84%)	46 (11.3%)	
Smoking status			0.432
No	113 (76.9%)	322 (79.3%)	
Yes	33 (22.4%)	76 (18.7%)	
Unknown	1 (0.68%)	8 (1.97%)	
Contraception category			0.001
Barrier	17 (11.6%)	88 (21.7%)	
Hormonal	62 (42.2%)	166 (40.9%)	
Non-hormonal	4 (2.72%)	31 (7.64%)	
None	64 (43.5%)	121 (29.8%)	
No. of infections			<0.001
Multiple episodes	3 (2.04%)	136 (33.5%)	
Single episode	144 (98.0%)	270 (66.5%)	

Table III *Entire Cohort of 553 Patients Stratified by One or More Culture-Confirmed* Mycoplasma/Ureaplasma *Infections*

	Recurrent N=139	Single episode N=414	p Overall
Mean age	26.0 [21.5; 33.0]	27.0 [23.0; 33.0]	0.339
Relationship status			0.233
Married	18 (12.9%)	73 (17.6%)	
Single	120 (86.3%)	340 (82.1%)	
Other	1 (0.72%)	1 (0.24%)	
Ethnicity			0.410
Asian	2 (1.44%)	13 (3.14%)	
Black/African American	31 (22.3%)	71 (17.1%)	
Hispanic	21 (15.1%)	51 (12.3%)	
White	73 (52.5%)	232 (56.0%)	
Unknown	12 (8.63%)	47 (11.4%)	
Smoking status			0.415
No	115 (82.7%)	320 (77.3%)	
Yes	23 (16.5%)	86 (20.8%)	
Unknown	1 (0.72%)	8 (1.93%)	
Contraception category			0.021
Barrier	27 (19.4%)	78 (18.8%)	
Hormonal	71 (51.1%)	157 (37.9%)	
Non-hormonal	8 (5.76%)	27 (6.52%)	
None	33 (23.7%)	152 (36.7%)	
Recurrence			<0.001
No	3 (2.16%)	144 (34.8%)	
Yes	136 (97.8%)	270 (65.2%)	

gle confirmed episode of *Ureaplasma/Mycoplasma*. 33.5% of cases who returned with recurrent symptoms were diagnosed with multiple episodes of *Ureaplasma/Mycoplasma* infections, which was statistically significant ($p<0.001$) (Table II). 86.3% of subjects with culture-confirmed recurrent *Mycoplasma/Ureaplasma* infections reported their relationship status as single (Table III). The distribution of ethnicities was also similar between subjects with recurrent and a single episode of *Ureaplasma/Mycoplasma*. Subjects who were diagnosed with recurrent *Ureaplasma/Mycoplasma* infections identified as White, Black/African American, Hispanic, and Asian at 52.5%, 22.3%, 15.1%, and 1.44%, respectively. Subjects who were diagnosed with a single episode of infection identified as White, Black/African American, Hispanic, and Asian at 56.0%, 17.1%, 12.3%, and 3.14%, respectively ($p=0.410$). 82.7% of subjects with recurrent *Ureaplasma/Mycoplasma* infections reported being non-smokers, as compared to 77.3% of subjects with a single infection ($p=0.415$).

The majority of the subjects with recurrent *Ureaplasma/Mycoplasma* infections reported using hormonal methods (51.1%), followed by no contraceptive use (23.7%), barrier methods (19.4%), and non-hormonal methods (5.76%). Subjects diagnosed with a single episode of *Ureaplasma/Mycoplasma* infection showed a similar pattern, reporting hormonal methods (37.9%), no contraceptive use (36.7%), barrier methods (18.8%), and non-hormonal methods (6.52%) (Table III).

Subjects were also analyzed by treatment and concurrent infections such as bacterial vaginosis (BV), yeast, and human papillomavirus (HPV) (Table IV). Only subjects with a single episode of *Mycoplasma/Ureaplasma* infection were included in this analysis as subjects with multiple episodes of infections were associated with multiple treatments, repeat culture results, and coinfections, skewing data analysis. Of 414 subjects with a single episode of *Mycoplasma* and/or *Ureaplasma* infection, 13.5% had double (*Mycoplasma+Ureaplasma*) infections. The majority of the subjects were treated with Doxycycline (96.7%), and repeat cultures were negative in 53.1% of the subjects and positive in 5.56%. For the remaining majority, repeat cultures were not performed (41.1%).

Of analyzed subjects with recurrent vaginitis by our study definition and a single episode of *Ureaplasma/Mycoplasma* infection, 41.0% were concurrently positive for BV and 9.72% were positive for yeast (Table V). These rates of coinfection were statistically significant. 9.72% of sub-

Table IV *Demographics and Comorbidities of 414 Patients with a Single Episode of Culture-Confirmed* Mycoplasma/Ureaplasma *Infection*

	N=414	N
Mean age	29.5 (9.82)	414
Ethnicity		414
Asian	13 (3.14%)	
Black/African American	71 (17.1%)	
Hispanic	51 (12.3%)	
White	232 (56.0%)	
Unknown	47 (11.4%)	
Relationship status		414
Married	73 (17.6%)	
Single	340 (82.1%)	
Other	1 (0.24%)	
Smoking status		414
No	320 (77.3%)	
Yes	86 (20.8%)	
Unknown	8 (1.93%)	
Contraception category		414
Barrier	78 (18.8%)	
Hormonal	157 (37.9%)	
Non-hormonal	27 (6.52%)	
None	152 (36.7%)	
Single vs. double infection		414
Double (*Mycoplasma and Ureaplasma*)	56 (13.5%)	
Single (*Mycoplasma* or *Ureaplasma*)	358 (86.5%)	
Other Coinfections		
Concurrent BV		414
Negative	179 (43.2%)	
Positive	202 (48.8%)	
Not tested	33 (7.97%)	
Concurrent yeast		414
Negative	314 (75.8%)	
Positive	67 (16.2%)	
Not tested	33 (7.97%)	
Recurrence		414
No	144 (34.8%)	
Yes	270 (65.2%)	
Treatments		414
Azithromycin	2 (0.48%)	
Doxycycline	396 (95.7%)	
Levaquin	2 (0.48%)	
Vibramycin	13 (3.14%)	
Unknown	1 (0.24%)	
Repeat cultures (cure rate)		414
Negative	220 (53.1%)	
Positive	23 (5.56%)	
No repeat cultures	170 (41.1%)	

jects were found to be concurrently positive for HPV; however, a majority of the subjects were not tested for HPV due to being younger than 30 years old (57.6%), and most of them had normal Pap smears (77.1%).

Discussion

The prevalence of *Ureaplasma/Mycoplasma* for symptomatic women noted in this ambulatory site was similar to that in data collected by other authors (Taylor-Robinson). It is this subset of women who present for recurrent vaginitis, often diagnosed with bacterial vaginosis or yeast, who may have a higher prevalence of *Mycoplasma/Ureaplasma*.

There were no significant differences in the rates of recurrent vaginitis for women based on ethnicity, race, or marital status. Although the data indicate statistically significant findings in rates of vaginal infection for women who use hormonal contraception, this analysis should be taken in context. Most of the women who met criteria for our study, comparably to national averages, use hormonal interventions.[9] The value of statistical significance likely reflects our study population's preference for these types of contraceptives as opposed to a causative relationship between hormones and recurrent vaginal infections. Moreover, prior research suggests that levonorgestrel IUDs do not significantly affect the vaginal microbial balance.[10] Only a small percentage of our patients used non-hormonal IUDs.

As we hypothesized, many women with recurrent vaginitis, as defined by our study, did have *Ureaplasma/Mycoplasma*. 41.0% were concurrently positive for bacterial vaginosis, and 9.72% were positive for yeast (Table V). A limitation of our study in defining prevalence of *Mycoplasma/Ureaplasma* in the outpatient setting is the lack of standardized testing criteria for *Ureaplasma/Mycoplasma* among the providers of the practice in which the study was carried. Of the visits coded for vaginitis that were reviewed, not all patients were routinely tested for *Ureaplasma/Mycoplasma*, and the decision for testing was up to the clinical discretion of the provider. Most patients who were tested were returning patients with recurrent vaginitis symptoms within the same year or annually; however, this was not standard among all providers.

This retrospective chart review aims to redefine recurrent vaginitis and highlights the need to search for additional vaginal microbes that could cause persistent symptoms in women even after treatment. Current CDC recommendations define recurrent vaginitis as 4 or more infections in 1 year. Since over-the-counter self-treatment options are readily available, many women do not present for office visits when they have symptomatic vaginal

Table V *414 Patients with a Single Episode of Culture-Confirmed* Mycoplasma/Ureaplasma *Infection Stratified by Self-Reported Recurrence*

	No N=144	Yes N=270	p Overall
Mean age	27.0 [22.0; 33.0]	27.0 [23.0; 33.8]	0.753
Ethnicity			0.106
Asian	9 (6.25%)	4 (1.48%)	
Black/African American	26 (18.1%)	45 (16.7%)	
Hispanic	17 (11.8%)	34 (12.6%)	
White	79 (54.9%)	153 (56.7%)	
Unknown	13 (9.03%)	34 (12.6%)	
Relationship status			0.187
Married	29 (20.1%)	44 (16.3%)	
Single	114 (79.2%)	226 (83.7%)	
Other	1 (0.69%)	0 (0.00%)	
Smoking status			0.423
No	111 (77.1%)	209 (77.4%)	
Yes	32 (22.2%)	54 (20.0%)	
Unknown	1 (0.69%)	7 (2.59%)	
Contraception category			<0.001
Barrier	16 (11.1%)	62 (23.0%)	
Hormonal	61 (42.4%)	96 (35.6%)	
Non-hormonal	3 (2.08%)	24 (8.89%)	
None	64 (44.4%)	88 (32.6%)	
Single vs. double infection			0.130
Double (*Mycoplasma* and *Ureaplasma*)	25 (17.4%)	31 (11.5%)	
Single (*Mycoplasma* or *Ureaplasma*)	119 (82.6%)	239 (88.5%)	
Concurrent BV			<0.001
Negative	62 (43.1%)	117 (43.3%)	
Positive	59 (41.0%)	143 (53.0%)	
Not done	23 (16.0%)	10 (3.70%)	
Concurrent yeast			<0.001
Negative	107 (74.3%)	207 (76.7%)	
Positive	14 (9.72%)	53 (19.6%)	
Not done	23 (16.0%)	10 (3.70%)	

infections. In this case, the true number of recurrent infections based on the current definition is unlikely to represent the true number of women who have recurrent symptomatic infections since women will have often attempted to treat their symptoms on their own prior to presentation. We suggest that if a woman has persistent vaginitis symptoms and she needs a physical examination more than 1 time a year or returns for continued symptoms in subsequent years, there may be additional pathogens that need to be addressed.

References

1. Pizzorno JE, Murray MT, Joiner-Bey H: Vaginitis. *In* The Clinician's Handbook of Natural Medicine. Third edition. St. Louis, Elsevier, 2016, pp 945–959
2. Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. Available at https://www.cdc.gov/std/tg2015/candidiasis.htm. Updated 2015. Accessed May 11, 2019
3. O'Dowd TC, West RR, Ribeiro CD, et al: Contribution of Gardnerella vaginalis to vaginitis in a general practice. Br Med J (Clin Res Ed) 1986;292(6536):1640-1642
4. Taylor-Robinson D: Mollicutes in vaginal microbiology: Mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum and Mycoplasma genitalium. Res Microbiol 2017;168:875-881
5. McCormack WM: Ureaplasma urealyticum: Ecologic niche and epidemiologic considerations. Pediatr Infect Dis 1986;5(6 Suppl):S232-S233
6. Horner P, Taylor-Robinson D, Pallecaros A, et al: Int J STD AIDS 2019;30(3):310-311
7. Rumyantseva T, Khayrullina G, Guschin A, et al: Prevalence of Ureaplasma spp. and Mycoplasma hominis in healthy women and patients with flora alterations. Diagn Microbiol Infect Dis 2019;93:227-231
8. Marovt M, Kese D, Kotar T, et al: Ureaplasma parvum and Ureaplasma urealyticum detected with the same frequency among women with and without symptoms of urogenital tract infection. Eur J Clin Microbiol Infect Dis 2015;34(6):1237-1245
9. Kavanaugh ML, Jerman J: Contraceptive method use in the United States: Trends and characteristics between 2008 and 2014. Contraception 2018;97(1):14-21
10. Achilles SL, Austin MN, Meyn LA, et al: Impact of contraceptive initiation on vaginal microbiota. Am J Obstet Gynecol 2018;218:622.e1–622.e10