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A pilot study on *Trichomonas vaginalis* in women with recurrent urinary tract infections



Po-Chih Chang, Yu-Chao Hsu, Ming-Li Hsieh, Shih-Tsung Huang, Hsin-Chieh Huang, Yu Chen*

Department of Urology, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan

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ABSTRACT

Background: Trichomoniasis and recurrent urinary tract infections (UTIs) shared similar risk factors, age distribution and overlapping symptoms. The aim of this study was to determine the prevalence of *Trichomonas vaginalis* (TV) in women with recurrent UTIs, attending a urology clinic in a medical center, in order to inform screening and treatment policies. **Methods:** Women with recurrent UTIs, defined as the presence of lower urinary tract symptoms (dysuria, frequency and urgency) and three positive urine cultures on voided urine specimens in the previous year, were enrolled prospectively from January 2013 to April 2014. Urine samples were collected for culture and tested for TV using immunochromatographic strip. Outpatient follow-up was arranged to diagnose any symptomatic UTI recurrence.

Results: Sixty-five women were recruited. Mean age was 57.4 ± 14.3 year-old and follow-up duration was 9.5 ± 4.0 months. The prevalence of TV was 16.9% (11/65). Eight women had UTI recurrence in the follow-up period. Recurrence rate did not differ in patients with and without concomitant TV infection.

Conclusions: Given the high prevalence of TV, we suggest that testing for TV should be considered in women with recurrent UTIs. Further larger studies are needed to evaluate the potential benefit of treating TV in this group of patients.

* Corresponding author. Department of Urology, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan, Taoyuan 333, Taiwan. Tel.: +886 3 3281200; fax: +886 3 3285818.

E-mail address: yu.iok2681@gmail.com (Y. Chen).

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At a glance commentary

Scientific background on the subject

Trichomoniasis and recurrent urinary tract infections (rUTIs) shared similar risk factors, age distribution and overlapping symptoms. The prevalence of *Trichomonas vaginalis* (TV) infection in female patients with rUTIs, and the potential benefit of treating TV in them remain unknown.

What this study adds to the field

In the 65 patients with rUTIs, TV infection was found in 16.9% of them. Recurrence rate during the follow-up period did not differ in patients with and without TV infection. Given the high prevalence of TV, we suggest that testing for TV should be considered in women with rUTIs.

Trichomonas vaginalis (TV) is the most prevalent non-viral sexually transmitted infection (STI) in women [1]. According to the World Health Organization, over 248 million new cases of TV infections develop each year and around 8% of women are infected with TV worldwide [2]. Over 80% of TV infections are asymptomatic, however symptoms can appear weeks, months or even years after the initial infection [1,3]. Trichomoniasis is associated with a variety of adverse health effects including the acquisition and transmission of human immunodeficiency virus (HIV), infertility, pelvic inflammatory disease, cervical intraepithelial neoplasia, and preterm delivery [1,4–6]. Despite the large number of cases and the potentially severe health impact, it has long been regarded as a STI of minor importance from both clinical and public health points of view [3]. Unlike other STIs which are more frequently seen in the most sexually active women, the prevalence of TV peaks among women aged 51–60 years, followed by those aged over 60 years [7].

Urinary tract infections (UTIs) are the most common adult bacterial infections in the outpatient setting. Approximately 80% of all UTIs occur in women, and more than 50% of women experience at least one UTI during their lifetime [8]. Many women experience recurrence of a UTI within the first few months of the initial episode, with reported rates of recurrence ranging from 27% to 44% [9,10]. Postmenopausal women are more susceptible to recurrent UTIs due to the loss of the protective benefits of estrogen, with a resultant increase in vaginal pH and decrease in introital *Lactobacillus* colonization [11]. In the primary care setting, 53% of women above the age of 55 years and 36% of younger women report recurrence within 1 year [10]. Although several mechanisms have been postulated, managing women with recurrent UTIs remains a challenge because of increasing antimicrobial resistance and a lack of effective preventive methods.

In the era of modern diagnostic techniques, commercial kits using nucleic acid amplification and rapid antigen detection have been developed for a variety of diseases, including TV, and the quality of diagnosis has significantly

improved [6]. In our experience, some patients with a history of frequent UTIs are co-infected with TV, although they complain of only urinary symptoms. Given that these two diseases tend to occur in women of the same age group, we hypothesized that women with recurrent UTIs may have a higher prevalence of TV infection, and that treating the existing TV infection may decrease the recurrence of UTIs. The objective of this study was to investigate the prevalence of concomitant TV infections in a cohort of women with recurrent UTIs, and the potential benefit of treating the TV infection in these patients.

Materials and methods

From January 2013 to April 2014, women with a history of recurrent UTIs who visited our urological outpatient clinic in a tertiary hospital in northern Taiwan were prospectively enrolled. This study was approved by the Human Ethics Committee of our hospital (Chang Gung Medical Foundation Institutional Review Board, Permit No. 104-1533B). A recurrent UTI was defined as the presence of lower urinary tract symptoms (dysuria, frequency or urgency) and three positive urine cultures on voided urine specimens in the previous 12 months [12]. The patients visited the clinic due to a current UTI or for consultation for UTI problems during asymptomatic periods. All of the patients underwent a complete evaluation including a detailed history and a physical examination focusing on the urogenital system. Symptoms of overactive bladder (OAB), also known as urgency–frequency syndrome, were recorded according to the International Continence Society definition, which states “urgency, with or without urge incontinence, usually with frequency and nocturia [13].” Urine analysis and microscopic examination, bacterial cultures and urine *Trichomonas* rapid tests (Jei Daniel Biotech, Jinan, China) were performed on all patients. The *Trichomonas* rapid test kit is a US FDA-registered, immunochromatographic strip test using specific antibodies to detect *Trichomonas* protein antigens [6]. For the patients who tested positive for TV, metronidazole 500 mg orally twice a day for 1 week was prescribed. Other anti-bacterial antibiotics were also administered empirically or according to the latest sensitivity results available. The administration of antibiotics and/or metronidazole according to culture results continued if the patient had persistent symptoms of dysuria. Outpatient follow-up visits were scheduled for 4 weeks, 8 weeks and every 3 months thereafter. The patients were asked to repeat urine culture on follow-up visits if any UTI symptoms had recurred. If these follow-up cultures turned to be positive, the patients were considered to have recurrence of UTI during the follow-up period. In the patients who tested positive for TV, *Trichomonas* rapid tests were repeated for a test-of-cure 4 weeks after completing treatment.

A urine culture with at least 10^5 colony-forming units/mL of uropathogenic bacteria was considered significant. Commonly accepted uropathogens included enteric gram-negative rods, enterococci, *Staphylococcus saprophyticus* and group B streptococci [14]. We defined antibiotic resistant strains as those resistant to at least two kinds of different

Table 1 – Characteristics of the patients with recurrent urinary tract infections with and without concomitant *Trichomonas vaginalis* (TV) infections (n = 65).

Characteristics	All	With concomitant TV infection (n = 11)	Without concomitant TV infection (n = 54)	p Value
Mean age in years (SD)	57.4 (14.3)	53.2 (12.1)	58.3 (14.7)	.29
Mean follow-up duration in months (SD)	9.5 (4.0)	7.8 (5.2)	9.8 (3.6)	.12
Menopause	46 (70.8)	6 (54.5)	40 (74.1)	.17
Increased vaginal discharge/ leucorrhea	18 (27.7)	5 (45.5)	13 (24.1)	.07
OAB symptoms	35 (53.8)	4 (36.4)	31 (63.6)	.17
Symptomatic ^a	49 (75.4)	9 (81.8)	40 (74.1)	.29
Median days of symptom onset (range) ^b	7 (1–45)	10 (2–45)	7 (1–30)	.88
Dysuria ^b	42 (85.7)	8 (88.9)	34 (85.0)	.38
Frequency ^b	34 (69.4)	6 (66.7)	28 (70.0)	.42
Urgency ^b	19 (38.8)	4 (44.4)	15 (37.5)	.35
Hematuria ^b	14 (28.6)	1 (11.1)	13 (32.5)	.10
Microscopy on urine sediment				
RBC > 20/uL	20	5	15	.12
WBC > 30/uL	33	6	27	.39
Epithelial > 30/uL	3	2	1	.04
Bacteriuria	40	9	31	.13

Values are no. (%) of patients except as indicated.

Abbreviations: OAB: overactive bladder; RBC: red blood cell; WBC: white blood cell.

^a Patients having active symptoms of urinary tract infection when seeking medical help.

^b Values are no. (%) of symptomatic patients (n = 49).

antibiotics, including ampicillin, cephalosporin, fluoroquinolone or trimethoprim–sulfamethoxazole.

All patients were recruited for the prevalence survey. However, patients were excluded from analysis of the treatment outcome if they were diabetic or had other known neurogenic disorders, anatomical abnormalities, obstruction or malignancy of the urological system, and if they had previously undergone pelvic surgery or an anti-incontinence procedure. The patients who had been hospitalized for any etiology or urethral catheterization within 1 month were also excluded. However, the patients with asymptomatic upper urinary tract calculi with no obstructive uropathy who had not undergone an intervention in the past 12 months were not eliminated from the outcome analysis.

Data are presented as mean \pm standard deviation, median or percentage depending on the variable. Patient characteristic variables in each group were compared by one-way analysis of variance. The Student's t-test and chi-square test were used to compare differences between groups. A *p* value of less than .05 was considered to be statistically significant.

Results

A total of 65 women with recurrent UTIs were recruited for the prevalence survey. The mean age of these patients was 57.4 ± 14.3 years (range 24–90 years) and 70.8% (46/65) were postmenopausal. The follow-up duration was 9.5 ± 4.0 months. Eleven (16.9%) of the patients had concomitant TV infection and motile trichomonads were found on microscopic examination in 2 of them. Forty-nine women had a symptomatic UTI at the first visit. More than half (35/65,

53.8%) of the patients had had persistent OAB symptoms for a long time, and even in the interval between episodes of acute infection. The clinical characteristics of the patients with and without concomitant TV infections are shown in [Table 1].

Besides the typical UTI symptoms, 27.7% of the women complained of increased vaginal discharge and/or leucorrhea on examination, and this was the only clinical manifestation that differed between the women with and without concomitant TV infection, although the difference was not statistically significant (45.5% vs. 24.1%; *p* = 0.07). Gross hematuria was found in 28.6% of the symptomatic subjects, while microscopic hematuria was found in 45.5% of the TV infection group.

Urine cultures were positive for bacterial infection in 33 patients (50.8%), 6 of whom had more than one isolated microbe. One patient had a mycobacterial infection and one patient had funguria. *Escherichia coli* (*E. coli*) accounted for 76.9% (30/39) of all identified bacteria, and 60.6% (20/33) of the patients were infected by antibiotic resistant strains, 11 of which were *E. coli* with extended-spectrum β -lactamase [Table 2].

Nine diabetic patients were excluded from outcome analysis, and three patients with a history of pelvic surgery for colon cancer, endometrial cancer and urinary incontinence, and one patient with urinary tuberculosis were also excluded. In total, 52 women were eligible for outcome analysis. Eight (15.4%) cases had UTI recurrence during the follow-up period, 87.5% of whom were postmenopausal. Among the women with UTI recurrence during follow-up period, five were found to be infected with *E. coli* at the first visit. The clinical characteristics of the patients with UTI recurrence during the follow-up period are shown in [Table 3].

Table 2 – Bacteriology results of the patients with recurrent urinary tract infections with and without concomitant *Trichomonas vaginalis* (TV) infection (n = 65).

Urine culture result	All	With concomitant TV infection (n = 11)	Without concomitant TV infection (n = 54)
<i>Escherichia coli</i>			
Non-ESBL	19	1	18
ESBL	11	2	9
<i>Proteus mirabilis</i>	2	1	1
<i>Citrobacter diversus</i>	1	1	0
<i>Serratia marcescens</i>	1	0	1
Group B streptococcus	3	1	2
Enterococcus faecalis	1	0	1
Enterococcus durans	1	0	1
No bacterial growth	32	7	25

Abbreviation: ESBL: extended-spectrum beta-lactamases.

The presence of a concomitant TV infection, hematuria, a history of increased vaginal discharge/leucorrhoea, and OAB symptoms were not significantly different between the patients with and without recurrence during the follow-up period.

All of the 11 women with concomitant TV infections were treated with oral metronidazole. Two of them remained positive in a test-of-cure after the initial treatment, one of whom also had a UTI recurrence during the follow-up period.

Discussion

Although it has been identified in all ethnic groups and socioeconomic strata, the prevalence of trichomoniasis varies

Table 3 – Characteristics of the patients with recurrent urinary tract infections (UTIs) according to the presence of UTI recurrence during the follow-up period (n = 52).

Characteristics	Free of UTI recurrence (n = 44)	UTI recurrence (n = 8)	p Value
Mean age in years (SD)	54.5 (14.2)	60.8 (14.2)	.26
Postmenopausal	27 (61.4)	7 (87.5)	.15
Increased vaginal discharge/leucorrhoea	13 (29.5)	1 (12.5)	.32
OAB symptoms	25 (56.8)	2 (25)	.10
Hematuria	10 (22.7)	2 (25)	.89
Concomitant TV infection	8 (18.2)	1 (12.5)	.35
Isolation of <i>E. coli</i>	17 (38.6)	5 (62.5)	.13
Isolation of drug resistant bacteria from urine ^a	9 (20.5)	5 (62.5)	.09

Values are no. (%) of patients except as indicated.

Abbreviations: OAB: overactive bladder; TV: *Trichomonas vaginalis*; *E. coli*: *Escherichia coli*.

^a Bacteria that were resistant to at least two kinds of different antibiotics, including ampicillin, cephalosporin, fluoroquinolone or trimethoprim–sulfamethoxazole.

widely between different populations, ranging from 5.4% in family planning clinics, 17.3% in patients presenting to sexually transmitted disease clinics, to 32% among incarcerated women [3,15]. Reported risk factors for trichomoniasis include lower socioeconomic status, lower educational level, douching, and a higher number of lifetime sex partners [16,17]. Epidemiological data on trichomoniasis in Taiwan are scarce. A large scale survey on women undergoing routine Papanicolaou smears in urban Taiwan reported that the prevalence of TV was 1.88% [17], reaching as high as 3.77% among patients visiting sexually transmitted disease clinics. Another cross-sectional study of 269 women attending gynecologic clinics found that the prevalence of TV infection was 7.8% [18]. To the best of our knowledge, this study is the first to report that the prevalence of TV in women with recurrent UTIs is 16.9%, which is two to eight times higher than the reported prevalence of TV infection in other populations. This extremely high prevalence rate suggests that patients with recurrent UTIs are specifically at risk of TV infections, and the association between these two infections is of interest.

Several studies have postulated that TV may serve as a “vector” for the spread of other pathogens into the genitourinary tract in view of its ability to ingest *Neisseria gonorrhoeae*, *Mycoplasma*, other bacteria, and viruses [19–21]. In addition, in the pathogenesis of trichomoniasis, TV may cause local inflammation as the parasite attaches to the mucosa of the cervix, vagina and urethra. The secretion of cysteine proteinases, a cell-detaching factor, leads to exfoliation of epithelial cells and breakdown of the structural integrity and defense barrier of the urogenital tract, making the host more vulnerable to other urogenital infections, such as HIV [22]. It is possible that TV also makes the host more vulnerable to urogenital bacteria, thereby increasing the risk of recurrent UTIs for patients infected by TV. Therefore, the prevalence of TV among patients with recurrent UTIs is higher than in other populations. If TV is treated and the urogenital defense barrier is repaired, the risk of recurrent UTIs should be decreased.

Two main hypotheses have been put forward to explain the increased risk of recurrent UTIs in some women. The first suggests that the local defense mechanisms of these women are defective and render them more susceptible to periurethral colonization [10]. The second suggests that the first episode causes changes in host resistance [23]. In either case, it is possible that microbial virulence factors play a less important role in recurrent UTIs than in the first episode, and that a defective host resistance mechanism is of more importance. If either of these hypotheses is true, women with recurrent UTIs may be more vulnerable to other urogenital infections, including TV. Elimination of TV may not decrease the risk of subsequent UTIs.

In our 52 patients of recurrent UTIs, 15.3% (8/52) of them had UTI recurrence after treatment during the follow-up period. In order to minimize confounding factors, we excluded patients with diabetes and those with other urogenital or neurological abnormalities from the outcome analysis, so our recurrence rate is lower than previously reported. Several studies have shown that individuals with diabetes have an increased relative risk of UTIs compared to those without diabetes [24]. In the present study, five out of nine diabetic women had UTI recurrence during the follow-up

period. In addition, the patients infected with TV were not more likely to have UTI recurrence in the follow-up period (12.5% vs. 18%). For ethical reasons, all of the patients who tested positive for TV were treated. Breakdown of the local defense barrier may have been repaired after treating TV, resulting in the similar recurrence rate in the two groups. We could not conclude which of the above hypotheses is correct, and whether the tendency of having recurrent UTIs is caused by TV infection or determined by the host per se is unknown. Larger longitudinal cohort studies are needed to elucidate this issue.

Increased vaginal discharge/leucorrhea was more common in the patients with concomitant TV infection in this study. However, the association between symptomatic vaginal discharge and TV infection is controversial. In a population-based study, the prevalence of TV infection was not different between women with or without vaginal symptoms, including vaginal discharge, itching or odor [16]. In contrast, another study on women undergoing gynecological examinations revealed that those infected with TV were more likely to report vaginal discharge and leucorrhea [25]. However, only the women with leucorrhea diagnosed by microscopy were shown to have a 4-fold increased risk of TV infection in multivariate analysis. Because self-reported vaginal discharge is a rather non-specific symptom, microscopic examination of vaginal discharge may help define patients with pathologic leucorrhea, and may be needed in future studies.

The presence of hematuria has also been reported to be a strong predictor of recurrent UTIs [26]. Erythrocytes provide essential nutrients needed by TV such as fatty acids and iron [27]. Iron can be obtained by hemoglobin degradation after the lysis of erythrocytes, which also requires cysteine proteinase activity. In a clinical scenario, the symptoms and signs of TV infection can fluctuate and worsen around the time of menses [27]. Hematuria, either gross or microscopic, bears abundant erythrocytes and may foster the growth of these parasites. Microscopic hematuria was more frequently seen in our patients with TV infection compared with those without TV (45.5% vs. 27.8%), though the difference did not reach statistical significance.

According to the recommendations of the United States Centers for Disease Control and Prevention, all women seeking care for symptoms of vaginal discharge should be tested for TV infection [28]. However, the high rate of asymptomatic TV infections in women supports the idea that clinicians should not limit evaluations for trichomoniasis to symptomatic, more specifically vaginal discharge, patients alone [16]. Because UTIs and STIs share similar risk factors, age distribution and overlapping symptoms, it is usually difficult to differentiate these two infections merely by clinical manifestations [29,30]. Furthermore, several studies have demonstrated that around 20% of adult women with a culture-proven UTI have concomitant vaginal or cervical infection with sexually transmitted organisms, including TV [30]. In this pilot study, we found a higher prevalence of TV among the women with recurrent UTI. Therefore, to improve the detection and treatment of TV infection, we suggest that testing for TV should be considered for women with recurrent UTIs, and that there is a need for further larger scale studies to investigate the possible benefits of treating TV in these patients.

There are some limitations to this study. First, only immunochromatographic antigen tests were used to diagnose TV infection. It has been reported that compared with wet mount, the test kit used in this study (Jei Daniel Biotech, Jinan, China) has a sensitivity of 100% and specificity of 88% when used on urogenital specimens [31]. These point-of-care test kits are easy to perform and the results are quickly available, however the sensitivity is not as good as with nucleic acid amplification tests and some cases will be undiagnosed, especially those that are asymptomatic with presumably a lower organism burden [6]. The use of such kits may lead to underestimation of the true prevalence. Second, information on the patients' sexual history was minimal or lacking. We were unable to carefully assess the relationship between sexual intercourse and recurrent UTIs because of the reluctance of our patients to discuss sexual practices. Third, we do not have a control group of healthy female. However, compared with previously reported prevalence of TV in Taiwanese women undergoing routine smears, it is highly possible that women with recurrent UTIs do have higher prevalence of TV.

Despite these limitations, this report represents a relevant contribution to the epidemiology of TV among patients with recurrent UTIs. We suggest that women with recurrent UTIs are specifically at risk of TV infection. Screening and treatment strategies for these women should be established. Our findings also highlight the interaction between TV, uropathogenic bacteria and susceptible hosts. Future research focusing on these issues will enhance our understanding of trichomoniasis, and make effective prevention possible.

Conflicts of interest

The authors declare that they have no competing interests.

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