Original Article

Risk of urinary tract infection symptoms recurrence in women: A prospective observational study

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Abstract

Objectives: Urinary tract infection (UTI) symptoms recurrence is common with estimated rate of 30%–50% within 1 year. The study aimed to evaluate the potential risk factors for symptoms UTI recurrence in women at outpatient clinic in a prospective fashion. **Materials and Methods:** This study was conducted from July 1, 2016, to June 30, 2019. Women who visited urological clinics with symptoms suggestive of UTI were invited to fill the questionnaire including baseline characteristics and Urinary Tract Infection Symptom Assessment questionnaire. Mid-stream urine samples of the participants were collected for urine analysis and urine culture. Phone interviews were done at 12 months' postclinic visit to inquire if the participants have any episode of UTI symptoms recurrence during the period of time. **Results:** Among the 188 eligible patients, 183 patients (age = 50.0 ± 15.3 years old) were included in the analysis. There were 44 (24%) participants had UTI symptoms recurrent episodes during the 12-month follow-up. Further multivariate analysis revealed that menopause (odds ratio [OR] = 4.89, 95% confidence interval [CI] = 1.63–14.68, $P = 0.005$), history of UTI-related symptoms within 1 year before the episode OR = 3.79, 95% CI = 1.29–11.15, $P = 0.016$) and *Escherichia coli* infection (OR = 4.81, 95% CI = 1.51-15.28, $P = 0.008$) were significant risk factors for UTI symptoms recurrence during the 12 months' follow-up. **Conclusion:** Menopause, history of UTI-related symptoms within 1 year before this episode of UTI and *E. coli* infection in 12 months were potential risk factors for UTIs symptoms recurrence in women.

Introduction

*U*rinary tract infection (UTI) is one of the most common diseases worldwide in women which lead to 7 million office visits, 1 million emergency department visits, 100,000 hospitalizations and $1.6 billion in healthcare spend each year [1]. It was estimated that women have about a 60% lifetime risk of UTI with a 30%–50% recurrence risk annually [2,3]. Uncomplicated UTI is a relatively simple disease to manage and a 3-day antibiotics regimen is usually feasible for managing most patients. However, the high recurrence rate can lead to impaired quality of life and significant economic burden [4]. UTI symptoms recurrence is common and bothersome to women with a history of UTI. The pathophysiology of UTI symptoms recurrence is multifactorial which includes bacterial virulence, host susceptibility and incomplete treatment. Identifying those at higher risk of UTI symptoms recurrence and providing them with preventive strategies may greatly improve patient care, quality of life, and reduce antibiotic use to avoid increasing trends of antibiotic resistance. Thus, the aim of this prospective study was to evaluate the potential risk factors for UTI symptoms recurrence in women.

Materials and Methods

This prospective study was approved by the Institutional Review Board and Ethics Committee of the Taipei Tzu Chi Hospital on 21 January 2019 with registered number: 05-FS02-024. Women who visited urological clinics with symptoms suggestive of UTI between July 1, 2016, and June 30, 2019 were invited to participate in the study. All participants were informed about the study design and purpose. Written consent was obtained before enrollment. The participants were asked to fill out a questionnaire including baseline

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characteristics (including age, diabetes status, recent sexual activity, menopause status, and history of UTI-related symptoms episodes within 1 year), the Chinese version of the Urinary Tract Infection Symptom Assessment (UTISA) questionnaire and the Bristol stool scale. Bristol stool scale was classified into 7 types according to their texture and morphology. Patients with the type 1 or 2 stool type were considered constipated [5]. Patients who met the following criteria were enrolled into the study: (1) age between 20 and 80 years-old; and (2) UTISA symptom score >3 on the visit day. Patients were excluded if they had a history of urolithiasis, neurogenic bladder, previous antibiotic treatment for any disease within 1 week before enrollment, allergy to antibiotics, pregnant or currently breastfeeding, or were immune compromised.

A study nurse provided instructions to ensure that participants collected a sterile, mid-stream urine sample for urinalysis and urine culture. Empirical antibiotic treatment with Cephalexin 500 mg, 4 times per day for 7 days, was prescribed on the day of the clinical visit. Participants were asked to complete the UTISA symptom score on day 1 (UTISA1) and day 3 (UTISA3) for follow-up of UTI-related symptoms. The participants were requested to return to the clinic on day 7 and followed with urinalysis and UTISA symptom score (UTISA7) to evaluate treatment efficacy. Treatment success was defined as UTISA symptom score ≤ 3 and bacterial counts <100 counts/μL on urinalysis on day 7. Phone interviews were carried out at 12 months' posttreatment to inquire if the participants had any episode of UTI symptoms recurrence during the time period. The definition of a UTI symptoms recurrence episode was presence of symptoms of UTI (dysuria, frequency, and lower abdominal pain) that needed physician visit and taking at least 3 days of antibiotic treatment to relieve the symptoms.

MedCalc Statistical Software (version 16.1, MedCalc, Ostend, Belgium) was used for statistical analysis. Baseline characteristics data were analyzed with Chi-square tests (categorical variables), Mann–Whitney test (ordinal variable) and independent *t*-tests (continuous variables). Univariate logistic regression and multivariate logistic regression in a stepwise fashion were used to determine the potential risk factors for UTI symptoms recurrence in women. A $P < 0.05$ was considered statistically significant.

RESULTS

Of the 188 patients assessed for eligibility, 183 patients (mean age: 50.0 ± 15.3 years) were included in the study for analysis after excluding 5 patients with UTISA symptom score ≤ 3. Among the 183 patients, 44 (24.0%) participants had recurrent symptoms episodes of UTI during the 12 months' follow-up. Table 1 shows the baseline characteristics of the included patients and associated parameters.

Among 183 urine samples collected on the visit day, 4 urine cultures were not collected. The remaining 179 urine cultures yielded 95 *Escherichia coli*, 42 mixed growth, 8 *Proteus mirabilis*, 6 *Klebsiella pneumonia*, 5 *Citrobacter species*, 4 *Streptococci species*, 4 *Staphylococci species*, 4 Gram-positive cocci species, 3 group B *Streptococci species*, 3 *Lactobacillus species*, 1 g negative bacilli species, 1 *Enterobacter species*, 1 *Enterococci species*, 1 *Corynebacterium species*, 1 Gram-positive bacilli species. Table 2 summarizes the culture results.

Univariate analysis revealed that the significant risk factors of UTI symptoms recurrence were age (odds ratio [OR] =1.04, 95% confidence interval [CI] = 1.02–1.07, $P = 0.002$), history of childbirth (OR = 2.86, 95% CI = 1.24–6.61, $P = 0.014$), menopause (OR = 3.67, 95% CI = 1.64–8.22, $P = 0.002$), sexually active status (OR = 0.38, 95% CI = 0.19–0.75, $P = 0.006$), history of UTI-related symptoms within 1 year before this episode of UTI (OR = 3.02, 95% CI = 1.16–7.84,

Table 1: Baseline characteristics and clinical outcomes in women with uncomplicated urinary tract infection

	All patients (*n*=183; 100%), *n* (%)	Recurrence in 12 months (*n*=44; 24%), *n* (%)	No recurrence in 12 months (*n*=139; 76%), *n* (%)	*P*
Baseline characteristics				
Age	50.0±15.3	56.6±14.3	48.0±15.1	<0.001*
DM history	20 (10.9)	5 (11.4)	15 (10.8)	0.916
Menopause	104 (56.8)	34 (77.3)	70 (50.4)	0.003*
Childbirth history	121 (66.1)	36 (81.8)	85 (61.2)	0.012*
Abdominal surgery history	17 (9.3)	4 (9.1)	13 (9.4)	0.959
Hysterectomy history	29 (15.9)	10 (22.7)	19 (13.7)	0.153
Cranberry usage experience	78 (42.6)	18 (40.9)	60 (43.2)	0.793
Daily fluids consumption	1423.8±602.1	1501.1±647.6	1399.3±587.2	<0.0001*
Voiding postponement within 1 week	108 (59.0)	25 (56.8)	83 (59.7)	0.734
Daily urinary frequency within 1 week	8.9±4.7	9.4±5.6	8.7±4.4	<0.0001*
Sexual activity within 1 year	108 (59.0)	18 (40.9)	90 (64.8)	0.005*
Bristol constipation within 3 months	41 (22.4)	11 (25.0)	30 (21.6)	0.637
UTI-related symptoms history within 1 year	51 (27.9)	15 (34.1)	36 (25.9)	0.017*
Outcome				
Escherichia coli infections	95 (53.1)	28 (66.7)	67 (48.9)	0.064*

*P<0.05. Data are presented as *n* (%) or mean±SD as appropriate, comparing variables with recurrence using Chi-square or *t*-test as appropriate. UTI: Urinary tract infection, SD: Standard deviation, DM: Diabetes mellitus

P = 0.023) and *E. coli* infections (OR = 2.09, 95% CI = 1.01–4.31, *P* = 0.046).

Multivariate logistic regression analysis was performed in a stepwise fashion with parameters including history of diabetes mellitus, abdominal surgery, hysterectomy, voiding postponement within 1 week, sexually active status, cranberry usage and daily urinary frequency within 1 week, and chronic constipation defined by the Bristol stool scale. The results revealed that menopause (OR = 4.89, 95% CI = 1.63–14.68, *P* = 0.005), history of UTI-related symptoms within 1 year before this episode of UTI (OR = 3.79, 95% CI = 1.29–11.15, *P* = 0.016) and *E. coli* infections (OR = 4.81, 95% CI = 1.51–15.28, *P* = 0.008) were significant risk factors for UTI symptoms recurrence [Table 3].

Of 183 patients, 4 did not return for follow up and another 4 did not have a urinalysis on day 7. Of 175 patients

eligible for the assessment of treatment efficacy, 98 (56%) met the criteria of treatment success (UTISA7: 0.74 ± 0.97, bacterial count: 17.00 ± 18.72 counts/µL on urine analysis on day 7), while 77 (43%) met the criteria of treatment failure (UTISA7: 4.03 ± 3.79, bacterial count: 242.09 ± 493.31 counts/µL on urine analysis on day 7). Figure 1 depicts the difference of the UTISA symptom score from visit day to post visit day 7 between treatment success and failure group.

Antibiotic sensitivity tests were performed on 114 urine samples collected on visit day which yield Gram-negative uropathogens. The susceptibility rates of *E. coli* were 85.26% for cefazolin, 64.21% for trimethoprim-sulfamethoxazole, 30.53% for ampicillin, and 31.58% for ampicillin/sulbactam. Table 4 summarizes the drug susceptibilities for Gram-negative bacteria.

DISCUSSION

The American Urological Association, Canadian Urological Association and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction published a review article in 2019 and established the guideline for managing UTI symptoms recurrence in women. The guideline gave comprehensive and conducive treatment recommendations [6]. Nevertheless, the description and evaluation for risk factors of UTI symptoms recurrence were not well addressed. In our study, the participants included were primarily women. Our results demonstrated that menopause, history of UTI-related symptoms within 1 year and *E. coli* infections in 12 months were significant independent risk factors for UTI symptoms recurrence in women.

The results of the current study were in line with the previous study that menopause is one of the significant risk factors for UTI symptoms recurrence. Kim *et al*. stated that women experienced the menopause period and this estrogen deficiency would have the genitourinary syndrome of menopause (GSM) that influence the physiological reaction of labia, vagina, urethra, bladder and result in (1) genital symptoms, i.e. vaginal irritation/dryness, pruritus vulvae, (2)

Table 2: Bacterial morphology and culture results on day of visit

Bacterial growth of urine specimens	*n* (%)
Gram-negative rods	
Escherichia coli	95 (53.1)
Klebsiella pneumonia	6 (3.4)
Proteus mirabilis	8 (4.5)
Citrobacter spp.	5 (2.8)
Gram-negative bacilli	1 (0.6)
Enterobacter spp.	1 (0.6)
Gram-positive cocci	
Streptococci spp.	4 (2.2)
Staphylococci spp.	4 (2.2)
Enterococci spp.	1 (0.6)
Group B *Streptococci*	3 (1.7)
Gram-positive cocci	4 (2.2)
Mixed growth	42 (23.5)
Gram-positive rods	
Lactobacillus spp.	3 (1.7)
Corynebacterium spp.	1 (0.6)
Gram-positive bacilli	1 (0.6)
Total	179

Table 3: Significant predictors of urinary tract infection symptoms recurrence in univariate and multivariate analysis

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.04 (1.02-1.07)	0.002*		
DM history	1.06 (0.36-3.10)	0.916		
Menopause	3.67 (1.64-8.22)	0.002*	4.89 (1.63-14.68)	0.005*
Childbirth history	2.86 (1.24-6.61)	0.014*		
Abdominal surgery history	0.97 (0.30-3.14)	0.956		
Hysterectomy history	1.86 (0.79-4.37)	0.156		
Cranberry usage experience	0.91 (0.46-1.81)	0.792		
Daily fluids consumption	1.00 (0.99-1.00)	0.328		
Voiding postponement within 1 week	0.89 (0.45-1.76)	0.734		
Daily urinary frequency within 1 week	1.03 (0.96-1.10)	0.418		
Sexual activity within 1 year	0.38 (0.19-0.75)	0.006*		
Bristol constipation within 3 months	1.21 (0.55-2.67)	0.636		
UTI-related symptoms history within 1 year	3.02 (1.16-7.84)	0.023*	3.79 (1.29-11.15)	0.016*
Escherichia coli infection	2.09 (1.01-4.31)	0.046*	4.81 (1.51-15.28)	0.008*

*P<0.05. UTI: Urinary tract infection, OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus

Table 4: Distribution of Gram-negative uropathogens and drug susceptibility

GNU	Susceptibility rate (%)																n (%)
	TMP-SMX	Amp	Amp/sb	Cfz	Ctx	Gent	Amk	Pip	Cip	Imp	Levo	Flo	Tig	Col	Dor	Cfp	
Escherichia coli	64	30	32	85	89	79	100	100	85	100	84	100	100	100	100	100	95 (84)
Proteus mirabilis	71	85	86	71	100	100	100	100	100	57	100	100	NT	NT	100	100	7 (6)
Klebsiella pneumoniae	67	0	0	67	100	83	100	100	100	100	100	83	67	33	100	67	6 (5)
Citrobacter koseri	100	0	0	100	100	100	100	100	100	100	100	100	NT	100	100	80	5 (4)
Enterobacter aerogenes	100	0	0	0	100	100	100	100	100	100	100	100	NT	100	100	NT	1 (1)
Total																	114

GNU: Gram-negative uropathogens, NT: Not tested, TMP-SMX: Trimethoprim-sulfamethoxazole, Amp: Ampicillin, Amp/sb: Ampicillin/sulbactam, Cfz: cefazolin, Ctx: ceftriaxone, Gent: Gentamicin, Amk: Amikacin, Pip: Piperacillin, Cip: Ciprofloxacin, Imp: Imipenem, Levo: Levofloxacin, Flo: Flomoxef, Tig: Tigecycline, Col: Colistin, Dor: Doripenem, Cfp: Cefoperazone
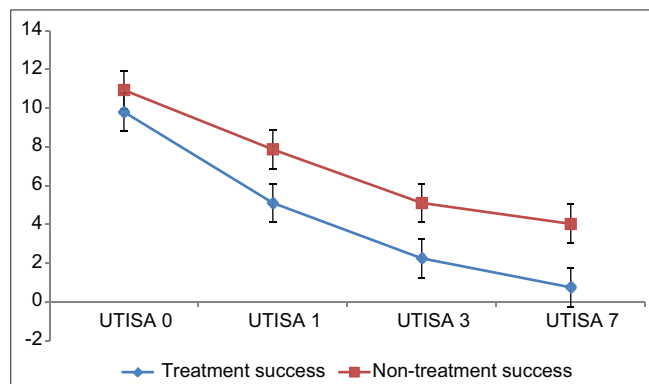

Figure 1: The UTISA symptom score form visit day to post visit day 7 between treatment success and nonsuccess group and showed by means of plot with SD of the mean. UTISA 0: UTISA symptom score on the visit day

sexual symptoms due to lack of lubrication, discomfort or pain, impaired function and (3) urinary symptoms, i.e. lower urinary tract symptoms (LUTS), urinary incontinence, UTI symptoms recurrence [7]. About 40%–54% of postmenopausal women suffered from GSM [8]. In our study, 34 of 44 (77.3%) women in menopause experienced a UTI symptoms recurrence within 12 months. The genitalia and lower urinary tract share common estrogen receptor function. Low levels or absence of estrogen leads to vaginal atrophy and reduced Lactobacillus species colonization that are responsible for maintaining vaginal acidity [9]. This effect provides natural protection for preventing the growth of pathogenic bacteria and UTI or vaginitis. Our results showed that aging was a significant risk in univariate analysis which was in line with the results by Suskind *et al*. [10]. The aging effect is not significant in multivariate analysis which implies that menopause may play a more significant role than aging. After delivery, change or damage to the genitourinary tract and pelvic floor support during peri-partum may be sustained and result in anatomical impairment such as stress urinary incontinence, levator ani damage, or ischemic urethral injury [11]. In our study, there was a trend that the women with childbirth history had a higher risk for UTI symptoms recurrence in univariate analysis, however, multivariate analysis did not demonstrate significant risk. So far, no studies have demonstrated the link between childbirth history and UTI symptoms recurrence. Whether these changes would persist and cause women to be vulnerable to UTI symptoms recurrence warrants further investigation.

History of prior UTI is also a significant risk factor for UTI symptoms recurrence in women [11]. About 30%–50% of women with UTI experienced annual symptoms recurrence [2,3]. The history of UTI is a broad array of topics, comprised of multiple factors (host, environment, bacterial virulence) which need to be discussed separately. Previous research mentioned that the age of first UTI occurrence before 15 years old, positive maternal UTI history [12], and previously documented *E. coli*-induced UTI [12,13] may each partially contribute to an individual's UTI symptoms recurrence. Due to the difficulty in obtaining detailed family medical records with formal diagnosis of UTI, we used the previous UTI-related symptoms within 1 year to represent the incidence of UTI within 1 year. According to the Tomas *et al*. study on women with LUTS, 48% had a positive urine culture with diagnosed UTI [14,15]. Nevertheless, because many urogenital diseases (i.e., vaginitis, overactive bladder and urinary incontinence) can present with LUTS and mimic UTI [14], future studies would require a more rigorous study design to include thorough exams and detailed medical history.

The most common uropathogens of UTI are *E. coli* (80%) followed by *Staphylococcus saprophyticus* (10%–15%), Klebsiella, Enterobacter, and Proteus species [16]. *E. coli* is a Gram-negative, rod-shaped bacterium, which normally resides in the lower gastrointestinal tract in humans [17]. Most of the strains are non-pathogenic except some uropathogenic *E. coli* (UPEC). The virulence factors, such as type 1 fimbriae, P fimbriae, Dr/Afa adhesins, facilitate UPEC adhere to mucosa. UPEC also secrete toxins, such as α-hemolysin, cytotoxic necrotizing factor 1, secreted autotransporter toxin, to impair the host's immunoreaction and enhanced bacterial invasion [18]. The two vital etiology for UTI symptoms recurrence are up stream infections (the fecal-perineal-urethral hypothesis) [16,19] and long – term bacterial colonization in the genitourinary tract [20]. Previous studies have stated that there were longer durations of UPEC vaginal colonization and three-fold more *E. coli* attached to vaginal, buccal, and voided uroepithelial cells in women with UTI symptoms recurrence compared to those without UTI symptoms recurrence [20].

Sexual activities have been linked to UTI symptoms recurrence for decades. It is believed that the most of the uropathogens originate from rectum, vagina, or periurethral area and then are introduced to the urinary tract during intercourse [12,21]. Younger women are more sexually active than other age groups, thus at highest risk for UTI symptoms

recurrence. Foxman *et al*. [21] stated that among 285 cohort female college students, vaginal intercourse within 2 weeks increased the risk of UTI symptoms recurrence (OR = 1.49, 95% CI = 1.08–2.06, *P* = 0.02), but no significant difference was seen with any contraceptive methods (condom, diaphragm, cervical cap, or spermicide). Scholes *et al*. [12] performed a case-control study (case subjects were 229 women aging 18–30 years old with UTI symptoms recurrence and control subjects were 253 randomly selected women with no UTI symptoms recurrence history) which demonstrated that recent 1-month intercourse frequency (OR = 5.8, 95% CI = 3.1–10.6), 12-month spermicide use (OR = 1.8, 95% CI = 1.1–2.9), and new sex partner during the past year (OR = 1.9, 95% CI = 1.2–3.2) were regarded as independent risk factors. In our study, we investigated the correlation between sexual activities within 1 year and UTI symptoms recurrences. The result in univariate analysis revealed significant lower risks while it became nonsignificant in multivariate analysis. The possible explanation may be due the fact that elderly women who were at higher risk of UTI symptoms recurrence were not as sexually active.

Chronic constipation was found to be associated with lower urinary tract dysfunction in pediatric field [22]. Hence, we tried to evaluate the relationship between constipation and UTI symptoms recurrence. The result of our study showed that a history of chronic constipation defined by the Bristol stool scale was not associated with a higher risk for UTI symptoms recurrence. Further research is warranted to correlate chronic constipation with UTI symptoms recurrence.

Nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin are available and considered as first-line treatment in the United States due to efficacy, and less adverse effect [6,23]. In 2010 updated guidelines by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, fluoroquinolone and β-lactam were classified as second-line therapy because of the high prevalence of local community resistance and lower efficacy than other agents respectively [23]. In Taiwan, guidelines for treating UTI suggest that nitrofurantoin, trimethoprim-sulfamethoxazole, first and second-generation cephalosporin and quinolone are all reasonable choices for first-line treatment. Ampicillin, ampicillin/sulbactam, fluoroquinolone are regarded as alternative treatment choices [24]. Previous study results showed that *E. coli* has lower susceptibility rates for trimethoprim-sulfamethoxazole (49%), ampicillin (30%), ampicillin/sulbactam (34%), but high susceptibility rate (81%) for cefazolin [25]. In our study, we had confidence for cefazolin efficacy due to high susceptibility rate record (>80%) against *E. coli* in our hospital experience. Hence, we prescribed Cephalexin as first line empirical antibiotic treatment. Hooton and Stamm [26] indicate that 3-day antibiotic therapy is sufficient for uncomplicated UTI, and is probably as effective as a 7–10 day therapy. Milo *et al*. [27] published a review article with 32 trials including 9605 patients in Cochrane Library, which states that 3 day therapy can achieve symptomatic relief similar to 5–10 day therapy. However, they emphasized that a 5–10 days' course may be considered curative as there is a better chance to eradicate the bacteriuria. Their treatment success rate was 57.54% for all participants (UTISA3: 3.55 ± 3.75).

There are several limitations in our study. First, the limited number of participants in this study was mainly collected from a single hospital. There may have existed selection, response and nonresponse bias. Second, the results of the biogram and susceptibility rate of the local area may not be widely applied to other regions or countries. Third, we investigated the experience of cranberry usage within 1 year by questionnaire without the further information of frequency and dosage. The strength of the study is its prospective nature which screened and followed these patients with questionnaire and urinalysis counted by a new fully automated urine particle analyzer.

CONCLUSION

UTI symptoms recurrence is common and easily encountered in the outpatient clinic. We conducted this observational study in a prospective fashion and followed these patients with questionnaires. We found that menopause, history of UTI-related symptoms within 1 year before this episode of UTI and *E. coli* infections in the past 12 months were potential risk factors for UTI symptoms recurrence in women.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Foxman B. Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. Dis Mon 2003;49:53-70.
2. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: Self-reported incidence and associated costs. Ann Epidemiol 2000;10:509-15.
3. Foxman B. Urinary tract infection syndromes: Occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am 2014;28:1-3.
4. Wagenlehner F, Wullt B, Ballarini S, Zingg D, Naber KG. Social and economic burden of recurrent urinary tract infections and quality of life: A patient web-based study (GESPRIT). Expert Rev Pharmacoecon Outcomes Res 2018;18:107-17.
5. Chumpitazi BP, Self MM, Czyzewski DI, Cejka S, Swank PR, Shulman RJ. Bristol Stool Form Scale reliability and agreement decreases when determining Rome III stool form designations. Neurogastroenterol Motil 2016;28:443-8.
6. Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. J Urol 2019;202:282-9.
7. Kim HK, Kang SY, Chung YJ, Kim JH, Kim MR. The recent review of the genitourinary syndrome of menopause. J Menopausal Med 2015;21:65-71.
8. Gandhi J, Chen A, Dagur G, Suh Y, Smith N, Cali B, et al. Genitourinary syndrome of menopause: An overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol 2016;215:704-11.
9. Amabebe E, Anumba DO. The vaginal microenvironment: The physiologic role of *Lactobacilli*. Front Med (Lausanne) 2018;5:181.
10. Suskind AM, Saigal CS, Hanley JM, Lai J, Setodji CM, Clements JQ, et al. Incidence and management of uncomplicated recurrent urinary tract

infections in a National sample of women in the United States. Urology 2016;90:50-5.

11. Guglietta A. Recurrent urinary tract infections in women: Risk factors, etiology, pathogenesis and prophylaxis. Future Microbiol 2017;12:239-46.

12. Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. J Infect Dis 2000;182:1177-82.

13. Foxman B, Zhang L, Tallman P, Palin K, Rode C, Bloch C, et al. Virulence characteristics of *Escherichia coli* causing first urinary tract infection predict risk of second infection. J Infect Dis 1995;172:1536-41.

14. Nik-Ahd F, Lenore Ackerman A, Anger J, Recurrent urinary tract infections in females and the overlap with overactive bladder. Curr Urol Rep 2018;19:94.

15. Tomas ME, Getman D, Donskey CJ, Hecker MT. Overdiagnosis of urinary tract infection and underdiagnosis of sexually transmitted infection in adult women presenting to an emergency department. J Clin Microbiol 2015;53:2686-92.

16. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. Dis Mon 2003;49:71-82.

17. Tenaillon O, Skurnik D, Picard B, Denamur E. The population genetics of commensal *Escherichia coli*. Nat Rev Microbiol 2010;8:207-17.

18. Lüthje P, Brauner A. Virulence factors of uropathogenic *E. coli* and their interaction with the host. Adv Microb Physiol 2014;65:337-72.

19. Yamamoto S, Tsukamoto T, Terai A, Kurazono H, Takeda Y, Yoshida O. Genetic evidence supporting the fecal-perineal-urethral hypothesis in cystitis caused by *Escherichia coli*. J Urol 1997;157:1127-9.

20. Stapleton A. Prevention of recurrent urinary-tract infections in women. Lancet 1999;353:7-8.

21. Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P, et al. Risk factors for second urinary tract infection among college women. Am J Epidemiol 2000;151:1194-205.

22. Yang S, Chua ME, Bauer S, Wright A, Brandström P, Hoebeke P, et al. Diagnosis and management of bladder bowel dysfunction in children with urinary tract infections: A position statement from the International Children's Continence Society. Pediatr Nephrol 2018;33:2207-19.

23. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52:e103-20.

24. Infectious Diseases Society of the Republic of China; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; Lee CY's Research Foundation for Pediatric Infectious Diseases and Vaccine. Guidelines for antimicrobial therapy of urinary tract infections in Taiwan. J Microbiol Immunol Infect 2000;33:271-2.

25. Chen LF, Chiu CT, Lo JY, Tsai SY, Weng LS, Anderson DJ, et al. Clinical characteristics and antimicrobial susceptibility pattern of hospitalized patients with community acquired urinary tract infections at a regional hospital in Taiwan. Healthc Infect 2013;19:20-5.

26. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. Infect Dis Clin North Am 1997;11:551-81.

27. Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev 2005;(2):CD004682.