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.

Keywords: Diagnosis, Laser flow cytometry, Recurrence, Urinary tract infection, Women
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. Participants 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 *Corynebacterium 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 childhood (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, 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

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

| Baseline characteristics | All patients (n=183; 100%), n (%) | Recurrence in 12 months (n=44; 24%), n (%) | No recurrence in 12 months (n=139; 76%), n (%) | P |
|--------------------------|----------------------------------|------------------------------------------|-----------------------------------------------|---|
| 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±660.2 | 1501.1±647.6                  | 1390.3±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*                                       |
| *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
**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)               | 0.023*                          |                                |                                 |
| 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
Amp/sb

Levo

100

100

85

100

100

100

100

83

100

0

100

67

32

Non-treatment success

E. coli

Dor

100

100

100

114

Col

NT

100

100

85

100

100

100

100

71

80

79

E. coli

100

100

100

100

100

100

100

100

83

100

67

33

100

67

6 (5)

30

7 (6)

100

100

100

100

100

100

100

100

71

80

5 (4)

100

100

100

100

100

100

100

100

114

Total

114

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, α-hemolysin, cytotoxic necrotizing factor I, 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 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 adsheins, 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].

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

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

| GNU | TMP-SMX | Amp | Amp/sb | Cfx | 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 | 95 (84) |
| Proteus mirabilis | 71 | 85 | 86 | 71 | 100 | 100 | 100 | 100 | 100 | 100 | 57 | 100 | 100 | NT | NT | NT | 100 | 7 (6) |
| Klebsiella pneumoniae | 67 | 0 | 0 | 67 | 100 | 83 | 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 | 80 | 5 (4) |
| Enterobacter aerogenes | 100 | 0 | 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | NT | 100 | NT | 1 (1) |

GNU: Gram-negative uropathogens, NT: Not tested, TMP-SMX: Trimethoprim-sulfamethoxazole, Amp: Ampicillin, Amp/sb: Ampicillin/sulbactam, Cfx: 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
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E. coli

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.

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