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Sporadic Compared to Recurrent Urinary Tract Infections: Considerations for Urogynecologic Patients

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Abstract

Aims: To describe the uropathogens and antimicrobial resistance patterns in women with singular, sporadic urinary tract infection (UTI) versus those with recurrent UTI (rUTI) in a urogynecologic population.

Methods: This was a cross-sectional analysis of women treated for a UTI by a urogynecologic provider in a one-year time frame. Subjects were divided into two groups: 1) sporadic UTI - no history of rUTI and a single infection in the study timeframe and 2) rUTI - history of rUTI and 2 UTIs in the study time frame. Our primary outcome was the difference in uropathogens between

groups. Secondary aims were to investigate host characteristics associated with recurrent *E.coli* infections and resistant uropathogens in the rUTI cohort.

Results: We had 265 women with 163 (61.5%) in the sporadic UTI group and 102 (38.5%) in the rUTI group. The most common uropathogens were *E. coli* (57.3%) and *Klebsiella* (11.7%). In the rUTI group, only 27/102 (26.5%) had all *E. coli* infections. There were differences between groups regarding age ($p=0.03$) and proportion of neurogenic bladder ($p=0.01$), intermittent self-catheterization ($p<0.01$), antibiotic suppression ($p<0.01$) and vaginal estrogen therapy ($p<0.01$). In the rUTI cohort, there were no risk factors that were significantly associated with recurrent *E.coli* UTIs and vaginal estrogen therapy was associated with a higher-odds of sensitive uropathogens (aOR 3.12; CI 1.28-7.56).

Conclusions: In those with rUTI, it was uncommon to have recurring *E.coli* UTIs and consistently sensitive uropathogens. Pre-treatment urine cultures are important to verify causative uropathogens in this population.

Keywords

Escherichia coli; Uropathogen

Introduction

Urinary tract infections (UTI) are one of the most common bacterial infections among women of all age groups.¹ It is estimated that up to 1 out of every 3 women has had at least one episode of UTI requiring antimicrobial therapy by 24 years of age, with the lifetime risk being greater than 50%.^{1,2} Within this population exists a subgroup of women prone to recurrent UTIs (rUTI), defined as 3 culture proven infections within a 12 month period, or 2 in a 6 month period.³ Incidence of rUTI has a bimodal age distribution, with highest frequency among women aged 18-34, and >55 years old.⁴ Major risk factors for UTI include sexual activity and a history of UTI, but the factors predisposing older women to rUTIs have been studied as well as those for younger, premenopausal women.⁵

The pathogenesis of rUTIs in older, postmenopausal women may be related to the microbial changes in the vagina associated with menopause. Lower systemic and local estrogen levels raise the vaginal pH and decrease the lactobacillus dominant vaginal flora typical for premenopausal women. Together, these factors increase the chance that microbes with uropathogenic capability establish residence in the vagina.⁶ There are mixed results in the literature regarding the impact of menopausal status on uropathogen prevalence and antimicrobial resistance profiles^{7,8} and further investigation is necessary.

In younger women, *E.coli* is the most common uropathogen, responsible for approximately 80% of UTIs,¹ and classically, the bacteria that cause rUTI are thought to be like those that cause sporadic infection (i.e., *E. coli*). However, non-*E. coli* infections are considerably more common in those with complicated UTIs, which include infections extending beyond the bladder,^{9,10} and other uropathogens, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, may be increased in certain populations.¹¹ While the epidemiology and pathogenic mechanisms of uropathogenic *E. coli* have been extensively studied,¹² little is

known about the associations between other uropathogens and the risk factors for their acquisition.

There is limited literature that suggests a lower incidence of *E.coli* UTIs in some groups of urogynecologic patients, such as those post-pelvic organ prolapse surgery.¹³ Historically, empiric therapy without confirmatory culture for singular episodes of acute cystitis was acceptable for non-pregnant, younger patients.¹⁴ What is not clear is if the uropathogen prevalence and susceptibility patterns are different in urogynecologic patients who experience sporadic infections as compared to those with recurrent infections. With recent guidelines suggesting pre-treatment urine cultures for women with rUTI, it is important to delineate if this is a necessity in all urogynecologic patients. The aim of this study was to evaluate the different uropathogens and antimicrobial resistance patterns in women with rUTIs as compared to those with a singular, sporadic UTI. We hypothesized that in a urogynecologic population, there would be a lower proportion of *E. coli* UTIs in women with rUTI as opposed to those with a sporadic UTI. We secondarily sought to investigate unique host characteristics in the women with rUTI that were associated with frequent *E. coli* infections and resistant uropathogens. These data could help to direct empiric therapy or guidance on the necessity of pre-treatment urine cultures in this distinct population.

Materials and Methods

After Institutional Review Board approval, we performed a cross-sectional analysis of all women treated for a UTI at a tertiary care, Urogynecologic practice in a one-year timeframe. We used our electronic medical record to identify women who were evaluated by the Division of Urogynecology and had a CPT code(s) associated with urine culture (UCx) and antibiotic susceptibilities (i.e., 87088, 87181, etc) within the specified timeframe. Patient charts and detailed UCx results were then reviewed to document the uropathogen and antimicrobial resistance profile. Women with symptoms of UTI and negative standard UCx or women with asymptomatic bacteriuria were excluded from analysis. Diagnostic criteria for acute UTI included symptoms of dysuria, urinary frequency or urgency, and/or suprapubic pain and a UCx with $>10^{3-5}$ colony-forming units (CFUs/mL) of bacteria.^{15,16} Clinical and demographic data were also abstracted from the electronic medical record including age, BMI, race, smoking status, history of rUTI, and hormone replacement therapy among others. Subjects were divided into two groups based on their rUTI history and frequency of UTI: 1) sporadic UTI - no history of rUTI and a single infection in the study timeframe and 2) rUTI - history of rUTI and ≥ 2 UTIs in the study time frame. We excluded women with a clinical history of rUTI but less than 2 UTIs in the study time frame. Post-menopausal status was defined as either documented post-menopausal status or age ≥ 55 . Patients were considered to be performing clean-intermittent self-catheterization (CISC) even if they did so infrequently. Bacterial isolates were recorded. *Klebsiella pneumoniae* and *Klebsiella oxytoca* were combined for analysis. Our primary outcome was the difference in uropathogens between groups. Secondary aims were to investigate host characteristics associated with recurrent *E.coli* infections and resistant uropathogens specifically in the rUTI cohort. We defined a sensitive uropathogen as one with report of antimicrobial sensitivity to nitrofurantoin, trimethoprim/sulfamethoxazole and ciprofloxacin. Our

laboratory does not routinely report sensitivities to fosfomycin therefore we could not use this factor when defining sensitivities.¹⁷

Statistical analysis was performed using SPSS V25.0 (IBM, Armonk, NY). Results are presented as means with standard deviations (SD) for continuous, normally distributed variables. Medians with interquartile range are reported for continuous, non-normally distributed variables. Categorical variables are presented as counts and percentages. Chi-square test was used for comparison of proportions with either Student's t-test or Mann-Whitney U used for comparison of continuous variables. Multivariable logistic regression models were used to control for confounders. A $p < 0.05$ was considered statistically significant.

Results

There was a total of 265 women with an average age of 66.4 years (SD 12.5) and body mass index of 28.1 (SD 6.6). Most women were white (94.1%) and postmenopausal (88.6%). There were 163 (61.5%) women in the sporadic UTI group and 102 (38.5%) in the rUTI group. In comparing demographic variables between these two groups, women in the rUTI group were slightly older ($p = 0.03$), less likely to have prolapse ($p = 0.02$) or have post-operative UTIs ($p < 0.01$). They were more likely to have neurogenic bladder ($p = 0.01$) and be performing CISC ($p < 0.01$). (Table 1) Finally, the rUTI group was also more likely to be on antibiotic suppression ($p < 0.01$) and using vaginal estrogen therapy ($p < 0.01$)

In total, there were 471 urine cultures. Median number of UTIs in the rUTI group was 2 [IQR 2]. The most common uropathogens were *E. coli* (270, 57.3%), *Klebsiella* (71, 15.5%), *Enterococcus faecalis* (48, 10.2%), and *Proteus mirabilis* (17, 3.6%). In the rUTI group, only 27/102 (26.5%) had all *E. coli* infections, but 75 (73.5%) had at least one *E. coli* UTI. In the sporadic UTI group, 100 (61.3%) had an *E. coli* infection. (Table 2). In the rUTI group, there was, on average, a longer time between the 1st and 2nd UTI (median 72 days, IQR 97) as compared to the 2nd and 3rd UTI (median 41 days, IQR 56) and the 3rd and 4th UTI (median 42 days, IQR 46.5).

For our secondary aims, we investigated potential characteristics of subjects in the rUTI cohort that might be associated with repetitive *E. coli* UTIs as compared to those that had different uropathogens. Ultimately, there were no variables associated with a lower or higher odds of all *E. coli* infections, including antibiotic suppression ($p = 0.78$). (Table 3)

We also investigated the antibiotic resistance of bacteria in the rUTI cohort. As a reminder, we defined "antibiotic resistance" as resistance to nitrofurantoin, trimethoprim/sulfamethoxazole and ciprofloxacin. We found that sensitivity of *E. coli* to these common antimicrobials ranged from 53.8-70.3% (Table 4). There was not a significant difference in sensitivity of *E. coli* as the number of urine cultures increased. Stated otherwise, if a patient had four UTIs, there was not a significant difference in the resistance of the *E. coli* in the 4th urine culture as compared to the 1st. When combining the four most common uropathogens (*E. coli*, *Klebsiella*, *E. faecalis*, and *P. mirabilis*), the proportion of uropathogens sensitive to all 3 antibiotics was similar and ranged from 48-55%. A total of 68 (66.7%) subjects in the

rUTI cohort had at least one urine culture that was not sensitive to all three antibiotics. Vaginal estrogen therapy was the only variable significantly associated with a higher odds of a subject having all urine cultures be sensitive to the common antibiotics (aOR 3.12; 95% CI 1.28-7.56) when controlling for confounding variables (sexual activity, menopausal status, antibiotic suppression, and CISC).

Discussion

Within our Urogynecologic population, approximately 60% of women with a singular, sporadic UTI in the study time frame had *E. coli* as the causative uropathogen. In the rUTI group, upwards of 74% of women had at least one *E. coli* UTI due to the overall higher proportion of UTIs. However, only 26.5% of women in the rUTI group had all *E. coli* UTIs. There were no risk factors associated with recurrent *E. coli* UTIs, but vaginal estrogen therapy was associated with a higher-odds of having sensitive uropathogens in the rUTI cohort.

In our study, the overall incidence of *E. coli* UTI was significantly less than previously quoted risk of up to 80%.^{11,18} Our patient population was from a Urogynecology practice at a tertiary care center and were, therefore, more likely to be older and postmenopausal. Other studies have reported slightly lower proportions of *E. coli* UTIs in a similar Urogynecologic population,¹⁹ but there is a paucity of data characterizing the specific uropathogens and resistance profiles in postmenopausal women, specifically those with rUTI. Studies have previously stated that the incidence of *Klebsiella* infections increased with age, which is consistent with our findings.²⁰ It is interesting that other isolated bacteria in the overall cohort was not *Staphylococcus* species, specifically *S. epidermidis*, as this has been previously reported as the third most common bacterial isolate among women following *E. coli* and *Klebsiella*.²¹ Additionally, *S. saprophyticus* is associated with up to 5-15% of all UTIs, and this was not consistently isolated in our study population.²² In our population, other common bacteria were *Citrobacter* and *Enterococcus*. Tabibian et al., investigated host characteristics associated with uropathogens in a broad population and found that *Paeroginosa* infections were associated with recent antibiotics and concluded that there may be a selection for antibiotic-resistant uropathogens in those with rUTI.²³ Our data speaks to the fact that a urogynecologic population suffering from UTIs is unique and deserves dedicated research and management guidelines.

Recurrent UTI has been linked to non-*E. coli* UTIs in community acquired bacteriuria.²⁴ In our rUTI cohort, we did find that less than 30% had consistent *E. coli* infections and we were unable to delineate any characteristics associated with recurring *E. coli* opposed to other uropathogens. In our study, antibiotic suppression and vaginal estrogen therapy were not associated with a decreased odds of *E. coli* UTIs. Other studies have certainly shown that antibiotic suppression leads to induced resistance in genito-urinary flora,²⁵ but we did not find that antibiotic suppression was associated with an increase in resistance uropathogens in our rUTI cohort. Vaginal estrogen was interestingly associated with a decrease in the proportion of resistant uropathogens. We did not have a majority of women on vaginal estrogen therapy in either group therefore we cannot speak to the preventative nature of vaginal estrogen in our study. Additionally, we do not know, in our population, how many

women were on vaginal estrogen for a history of rUTI but were not having active infections. Studies have shown that self-start antibiotic therapy in women is commonly preferred by women with recurrent UTIs.²⁶ It is important to consider at least intermittent UCx with sensitivity analysis to adjust empiric therapy³ in this specific population with a more unique uropathogenic profile. This recommendation is echoed in the recent “AUA/SUFU Recurrent Uncomplicated UTIs in Women” guidelines.³

Finally, our population is unique in the high percentage of women performing clean-intermittent self-catheterization. Of note, this was not necessarily women with definitive neurogenic bladder. Some women may have performed for a short period of time if they were either had post-procedure urinary retention or were just performing as a part of clinical evaluation. Our findings must be interpreted considering this demographic finding as there were more subjects performing CISC in the rUTI group. Studies suggest that there may be a different microbiologic profile to the causative uropathogens in patients that perform CISC. A higher proportion of bacteria like *Klebsiella spp.*, *Enterococcus spp.*, and *Proteus spp.* have been noted.²⁷ In our population, when controlling for confounders, CISC was not related to a lower odds of *E.coli* infections in the rUTI cohort.

Although our data is not generalizable to a younger population suffering from acute cystitis, there is far less literature on postmenopausal women, particularly with rUTI, which is a strength of our study. We evaluated a well-characterized cohort and utilized detailed review of the medical record to investigate bacterial isolates along with thorough collection of clinically relevant variables. We took many factors into account including recent urogynecologic surgery, prolapse and pessary use. However, our study has several potential limitations that are inherent to retrospective data that should be taken into consideration. Although we collected data on other antibiotics, we did choose to define antimicrobial resistance based on a group of commonly prescribed antibiotics. As we did not have data on fosfomycin sensitivities, we chose to combine the commonly prescribed antibiotics instead of the three 1st line agents.¹⁷

Conclusions

This current study adds to the literature regarding older women with UTIs and their unique nature. In a urogynecologic population, there was an overall lower proportion of *E.coli* UTIs as compared to the reported rates in the literature. Women with a history of rUTIs were unlikely to have consistent, recurring *E. coli* UTIs, and this should be taken into consideration when considering empiric therapy. Finally, our local, site-specific resistance patterns will be helpful when considering treatment for our population and to help increase our understanding of uropathogen resistance patterns in urogynecologic patients.

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Table 1:

Demographic Variables and Uropathogens by UTI Group

	Sporadic UTI (n=163)	Recurrent UTI (n=102)	p-value
Age, y	65.0 (12.5)	68.5 (12.2)	0.03
BMI	29.6 (9.6)	28.9 (6.7)	0.36
Race			
Caucasian	157 (96.3%)	93 (91.2%)	0.08
Black	4 (2.5%)	6 (5.9%)	0.15
Diabetes	25 (15.3%)	15 (14.7%)	0.89
Current smoker	15 (9.2%)	8 (7.8%)	0.70
Former smoker	50 (30.7%)	39 (38.2%)	0.21
Sexually active	61 (37.4%)	31 (30.4%)	0.24
History of recurrent UTI	0 (0.0%)	100 (100.0%)	<0.01
Antibiotic suppression	0 (0.0%)	20 (19.6%)	<0.01
Postmenopausal	138 (84.7%)	93 (91.2%)	0.12
Hormone therapy	41 (25.3%)	54 (52.9%)	<0.01
Vaginal Estrogen	34 (20.9%)	43 (42.4%)	<0.01
Prolapse	61 (37.4%)	24 (23.5%)	0.02
Pessary	22 (13.5%)	16 (15.7%)	0.41
Neurogenic Bladder	2 (1.2%)	7 (6.9%)	0.01
CISC	12 (7.4%)	21 (20.6%)	<0.01
Postoperative UTI ⁺	22 (13.5%)	3 (2.9%)	<0.01
Post BTX-A UTI	8 (4.9%)	2 (2.0%)	0.22

BMI; body mass index, CISC; clean-intermittent self-catheterization, BTX-A; onabotulinum toxin A

Data presented as either mean (SD) or n (%)

⁺ Either post-operative, post-BTX-A, or baseline due to neurogenic bladder

Table 2:**Bacterial Isolates by UTI group**

Bacterial Isolate	Sporadic UTI	Recurrent UTI	p-value
All <i>E. coli</i>	100 (61.3%)	27 (26.5%)	<0.01
Any <i>E. coli</i>		75 (73.5%)	0.04
All <i>Klebsiella</i> *	12 (7.4%)	7 (8.9%)	0.88
Any <i>Klebsiella</i> *		37 (36.3%)	<0.01
All <i>Enterococcus</i>	25 (15.3%)	0 (0.0%)	<0.01
Any <i>Enterococcus</i>		20 (19.6%)	0.37
All <i>Proteus</i>	5 (3.1%)	2 (2.0%)	0.59
Any <i>Proteus</i>		8 (7.8%)	0.08
All <i>ESBL</i>	2 (1.2%)	0 (0.0%)	0.71
Any <i>ESBL</i>		5 (4.9%)	0.07

Data presented as either mean (SD) or n (%)

* Includes both pneumoniae and oxytoca

Table 3:Multivariable Regression Model of All *E.Coli* UTI in Urogynecologic Patients with History of Recurrent UTIs

Adjusted Odds Ratio (aOR) of All <i>E.Coli</i> UTI		
	aOR (95% CI)	p-value
Sexually active	0.97 (0.33-2.84)	0.95
Postmenopausal	2.99 (0.62-14.5)	0.17
CISC	0.40 (0.11-1.49)	0.17
Vaginal estrogen therapy	1.84 (0.73-4.63)	0.19
Antibiotic Suppression	1.18 (0.37-3.71)	0.78

UTI; urinary tract infection, CISC; clean-intermittent self-catheterization

Table 4

Antimicrobial Sensitivities of Most Common Uropathogens in the Recurrent UTI Cohort

	Sensitive *	Resistant
First Urine Culture (n=102)		
<i>Escherichia coli</i> (n=54)	31 (57.4)	23 (42.6)
<i>Klebsiella</i> (n=20)	10 (50.0)	10 (50.0)
<i>Proteus mirabilis</i> (n=5)	2 (40.0)	3 (60.0)
<i>Enterococcus faecalis</i> (n=9)	8 (88.9)	1 (11.1)
Second Urine Culture (n=102)		
<i>Escherichia coli</i> (n=53)	35 (66.0)	18 (34.0)
<i>Klebsiella</i> (n=21)	7 (33.3)	14 (66.7)
<i>Proteus mirabilis</i> (n=4)	1 (25.0)	3 (75.0)
<i>Enterococcus faecalis</i> (n=9)	5 (55.6)	4 (44.4)
Third Urine Culture (n=65)		
<i>Escherichia coli</i> (n=37)	26 (70.3)	11 (29.7)
<i>Klebsiella</i> (n=12)	5 (41.7)	7 (58.3)
<i>Proteus mirabilis</i> (n=3)	0 (0.0)	3 (100.0)
<i>Enterococcus faecalis</i> (n=4)	2 (50.0)	2 (50.0)
Fourth Urine Culture (n=39)		
<i>Escherichia coli</i> (n=26)	14 (53.8)	12 (46.2)
<i>Klebsiella</i> (n=8)	5 (62.5)	3 (37.5)
<i>Proteus mirabilis</i> (n=0)	NA	NA
<i>Enterococcus faecalis</i> (n=1)	1 (100.0)	0 (0.0)

* Sensitive considered antimicrobial sensitivity to nitrofurantoin, trimethoprim/sulfamethoxazole and ciprofloxacin

Data presented as n (%)