Risk Factors for Recurrent Urinary Tract Infection in Young Women

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To define host factors associated with an increased risk of recurrent urinary tract infection (RUTI), a case-control study was conducted in 2 populations: university women and health maintenance organization enrollees. Case patients were 229 women 18–30 years old with RUTIs; control subjects were 253 randomly selected women with no RUTI history. In a multivariate model, independent risk factors for RUTI included recent 1-month intercourse frequency (odds ratio [OR], 5.8; 95% confidence interval [CI], 3.1–10.6 for 4–8 episodes), 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). Two newly identified risk factors were age at first urinary tract infection (UTI) ≤15 years (OR, 3.9; 95% CI, 1.9–8.0) and UTI history in the mother (OR, 2.3; 95% CI, 1.5–3.7). Blood group and secretor phenotype were not associated with RUTI. In young women, risk factors for sporadic UTI are also risk factors for recurrence. Two predictors suggest that genetic/long-term environmental exposures also predispose to RUTI.

Among women 18–30 years old, the incidence of acute uncomplicated urinary tract infections (UTIs) is estimated to exceed 0.5 episodes per annum [1]. These infections are a major source of morbidity and health care costs in this population. Identified risk factors for such infections include sexual activity, spermicide-based contraception, and a history of previous UTIs [1–7]. Among the 6–8 million young women estimated to have acute cystitis each year [8], most have only single or sporadic episodes. However, some 25%–50% experience recurrent episodes [9] that result in repeated office visits, antimicrobial use, time lost from work, urologic evaluation, and other morbidity and costs [10–12]. These repeated infections generally occur in the absence of anatomic abnormalities in the urinary tract [10–13], but their epidemiology and associated risk factors have received little study. We conducted a case-control study in 2 populations of young women, university students and a population-based sample of health maintenance organization (HMO) enrollees, to evaluate host factors associated with an increased risk of frequent recurrent UTIs.

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All study protocols were reviewed and approved by the institutional review boards at the University of Washington and Group Health Cooperative of Puget Sound. Written informed consent was obtained from all study participants.

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Methods

Study settings. This study was conducted at 2 sites: the University of Washington Student Health Center (Seattle) and the Group Health Cooperative of Puget Sound (Seattle), an HMO. The University of Washington health center provides primary care services to ~85% of the ~40,000 students attending the University of Washington. At the time of the study, ~46,000 patient visits were made each year by women 18–30 years old. Group Health Cooperative serves ~475,000 enrollees. During study enrollment (April 1994–January 1997), ~37,500 enrollees were women 18–30 years old.

Study subjects. To select potential recurrent UTI (RUTI) case patients, we used computerized ambulatory care databases at each site, to select all women 18–30 years old with a UTI diagnosis during the preceding month. Once identified, we obtained additional data on each patient's eligibility, symptoms, and laboratory test results via medical record abstraction. Women were considered to meet the case definition for RUTI if they had experienced either ≥3 symptomatic UTI episodes in the past year (including the index infection) or 2 such episodes in the past 6 months. A UTI was defined as $\geq 10^3$ cfu/mL of a uropathogen in midstream urine culture from a woman experiencing ≥2 symptoms of cystitis (dysuria, urgency, frequency, suprapubic pain, or hematuria) or, in the absence of a culture, demonstration of pyuria on urinalysis and ≥2 urinary symptoms, as well as complete and rapid resolution of symptoms in response to antibiotic therapy for UTI. All case patients had to have ≥1 culture-confirmed UTI. We excluded episodes of asymptomatic bacteriuria and symptomatic episodes that failed to meet these criteria.

Our criteria for selection of a nonrecurrent control group were conservative and were based on several considerations. In our estimation, the clearest assessment of risk factors for RUTI would be accomplished by comparing women who were low on the continuum of infection with a group of women high on the continuum (i.e., women with recent multiple infections). In addition, 1 of our major aims was to evaluate the possible role of genetic factors

(blood group and secretor phenotypes) in the risk of RUTI; other studies of these exposures have used nonrecurrent comparison groups similar to ours [14]. We thus chose age-similar women who had no history of >1 UTI in any 12-month period and who had not had a UTI in the preceding 12 months. Women with a history of sporadic UTIs were not excluded as control subjects.

We identified potential control participants at the university clinic by randomly selecting age-eligible women (frequency matching to within 1 year) who had visited the clinic for reasons unrelated to a UTI during the previous month. At the HMO, we developed a population-based sampling frame, to randomly select control subjects monthly from among age-eligible enrollees. Potential case or control participants who had been pregnant during the previous 12 months were excluded from the study, as were women with known anatomic abnormalities of the urinary tract.

Data collection. Potential case patients and control subjects were selected and recruited each month as the automated data for the preceding month became available. All women who were identified and who met the record abstraction selection criteria were sent a letter describing the study and inviting their participation. Those willing to participate were screened further for eligibility by telephone and, if eligible, scheduled for a clinic visit.

At the clinic visit, study participants were interviewed and examined. A structured interview using CAPI technology (computer-assisted personal interview; Sawtooth Software, Evanston, IL) was administered by a single staff member at each site. In CAPI, all responses are entered directly into a computer, and wording for each item along with appropriate skip patterns and range checks are programmed into the study instrument to minimize errors and assure standard administration. The interview underwent extensive pretesting and revision before final programming. The interview included items on demographic characteristics (age, race/ethnicity, and marital status); medical history (past history of UTI, age at first UTI, history of UTI among female relatives, and chronic medical conditions); contraceptive history (methods used during the past 12 months and detailed information on spermicide exposures); sexual history (age at first intercourse, recent and total sex partners, new sex partners in the past year, sexually transmitted disease history, and recent frequency of intercourse); and other behaviors of interest, such as voiding patterns, fluid consumption, douching practices, and hot tub use. Data on behavioral factors were collected for the 1-year and for the 1-month intervals preceding the "reference date" (the date of the index UTI episode for case patients and the midpoint of the sampling month for control subjects). After the interview, we obtained a saliva sample to determine blood group antigen secretor status and a blood specimen to determine ABO, P, and Lewis blood types, as described elsewhere [15].

Analyses and statistical methods. All data analyses were conducted by using SAS statistical software (SAS Institute, Cary, NC). Initially, we characterized the 2 study populations with regard to demographic and other selected variables, comparing RUTI case and control participants at each site separately. We explored the data more fully by examining all items in the interview, as well as the laboratory data, for their association with recurrent infection, using graphical displays, transformations, categorizations, and interaction terms.

Subsequently, we constructed multivariate logistic regression models with case-control status as the outcome [16]. We first developed site-specific models, to examine the relative contributions of variables that were univariately associated with RUTI. Among variables that were highly correlated, we selected 1 variable to use in the model. This was usually the variable most strongly associated with the outcome, unless extremely low numbers in ≥ 1 cells made the model too unstable. The site-specific models then were evaluated for their potential to be combined into a final predictive model for the study group as a whole. To explore whether a more rigorous definition of RUTI would affect the associations seen in the larger group, we identified and analyzed a subset of women with a more severe recurrence pattern (i.e., women who had experienced ≥ 1 UTI for every year of sexual activity).

Results

Study population characteristics. During the recruitment period, we identified 671 women as potential case patients from the automated data. Of these, 364 (54%) were ineligible after chart review or telephone screening. Lack of a confirmatory culture for ≥ 1 RUTI episode or uropathogen colony counts $<10^3$ accounted for ~70% of potential case exclusions. Of the remaining 307 potential study case patients, 41 women (13%) declined to participate or failed to make their clinic visit, and study staff were unable to contact 37 (12%). In total, 229 women (75%) agreed to participate and completed clinic visits, 100 (75%) at the University Clinic and 129 (75%) at the HMO. Of 486 women selected as potential control subjects, 89 (18%) were ineligible, and 64 (16%) of the remaining 397 declined participation; we were unable to contact 76 (19%). In all, 253 (64%) completed clinic visits, 113 (63%) at the university clinic and 140 (65%) at the HMO.

Compared with the university women, women at the HMO were older and more likely to be married or living as married, to have been pregnant, and to report fair or poor health (table 1). More than 80% of women at both study sites were white. The median lifetime number of UTIs was 5 and 7 (range, 2–100) for the university and HMO case groups, respectively, and 0 (range, 0–10) for both control groups. Of the control subjects, 19% and 29% of women at the university and HMO, respectively, had experienced ≥ 1 UTI.

Risk factors for RUTIs. In both study populations, case patients differed markedly from control subjects with respect to a number of sexual activity variables (table 2). Any lifetime sexual activity and any sexual activity during the past year were the variables most strongly associated with risk of recurrence. There were no case women at either site who had never had sexual intercourse (vs. 11%–15% of control women), and very few case patients had not had intercourse during the past year ($\leq 2\%$ vs. 22%–25% of control subjects). Women in the case groups were also much more likely than control subjects to report ≥ 4 episodes of intercourse during the month preceding the reference date (94% vs. 47% at the university; 84% vs. 49% at the HMO). Substantially higher proportions of women in both case groups also reported having a new sex partner during

Table 1. Distribution of selected variables for case patients and control subjects.

Variable	University clinic, %		Health maintenance organization, %	
	Case patients (n = 100)	Control subjects (n = 113)	Case patients (n = 129)	Control subjects (n = 140)
Age, years				
18–20	30	36	23	19
21–25	56	47	36	33
26–30	14	17	41	48
Race/ethnicity				
White	74	87	81	89
African American	2	0	7	3
Asian/Pacific Islander	20	9[a]	8	6
Other	4	4	4	2
Marital status				
Married/living as married	18	16	43	44
Never married	80	82	48	54
Other	2	2	9	3
High school education	99	97	67	79[a]
Ever pregnant	14	13	46	27[a]
No. of prior UTIs, lifetime				
0	0	81	0	71
1–4	48	17	26	24
5–9	29	2	36	4
⩾10	22	0	38	1

NOTE. UTI, urinary tract infection.
[a] $P < .01$ for case patients vs. control subjects.

the preceding 12 months (64% vs. 41% at the university; 43% vs. 24% at the HMO).

RUTI case patients were more likely to report exposure to spermicides (59% vs. 36% and 52% vs. 34% at the university and HMO, respectively) and to oral contraceptives (70% vs. 55% and 61% vs. 42%, respectively) during the preceding year (table 2). Notably low proportions of both case patients and control subjects reported using a diaphragm or cervical cap; most spermicide exposure was due to the use of spermicidal condoms.

A higher proportion of case patients reported experiencing their first UTI at a young age (⩽15 years old), with 22% of case patients versus 6% of control subjects at the university and 20% of case patients versus 9% of control subjects at the HMO reporting such a history (table 2). Histories of kidney infection, bacterial vaginosis, and sexually transmitted diseases were also more common in case women than in control women. In addition, 47% of case patients versus 25% of control subjects at the university, and 46% of case patients versus 27% of control subjects at the HMO reported that their mothers had histories of UTI.

We noted few differences between case patients and control subjects in a wide variety of other behavioral exposures that have been reported or proposed as risk factors for RUTI. These included pre- and postcoital voiding, frequency of urination, wiping patterns, douching, use of hot tubs, frequent use of pantyhose or tights, and others shown in table 2. A few variables, including history of chronic medical conditions and diaphragm contraception, occurred too rarely at either study site to be well evaluated.

RUTI case patients did not differ notably from control subjects by blood group phenotype as determined by secretor status (nonsecretor status, 20% vs. 22% at the university; 27% vs. 20% at the HMO), Lewis antigen status, or combined Lewis antigen/secretor status (table 2). When we considered only the control women without any UTI history, as done in some previous studies [14, 17], 24% of university control subjects and 17% of HMO control subjects were nonsecretors.

Multivariate models. In the site-specific predictive models, the final significant estimates of risk in the 2 study populations were in the same direction and were often of similar magnitude. We thus fit the same final model for each site for greater ease of comparison (table 3). Given the similarities, we also developed a combined model that provided risk estimates for the entire study population (table 3).

Of the exposures that remained in the multivariate model as independent risk factors, the factor most strongly associated with RUTIs at both sites was frequency of intercourse in the month preceding the reference date (the most recent episode of recurrence for RUTI cases). For the 2 sites combined, the odds ratios (ORs) were 5.8 (95% confidence interval [CI], 3.1–10.6) for 4–8 episodes of intercourse and 10.3 (95% CI, 5.8–18.3) for ⩾9 episodes of intercourse (table 3). Other behavioral factors that were independently associated with risk of being a case patient were spermicide exposure during the preceding year (OR, 1.8; 95% CI, 1.1–2.9) and having a new sex partner during the preceding year (OR, 1.9; 95% CI, 1.2–3.2). Second in magnitude only to frequency of intercourse were 2 nonbehavioral risk factors that remained in the model: age at first UTI ⩽15 years (OR, 3.9; 95% CI, 1.9–8.0) and a history of UTI in the mother (OR, 2.3; 95% CI, 1.5–3.7).

When we examined how these variables performed in a high-risk subset of our case group (women who had ⩾1 UTI episode for every year of sexual activity), we observed slightly stronger associations for the identified predictors. Personal and family histories of UTI showed the greatest increases: OR, 5.2 (95% CI, 2.5–11.2) for young age at first UTI and OR, 2.9 (95% CI, 1.7–5.0) for a reported history of infection in the mother (data not shown).

Discussion

Studies of RUTI to date have been largely descriptive and have focused primarily on the timing of recurrences, the genetic identity of the infecting strains, and on both bacterial virulence determinants and host epithelial cell characteristics that may increase susceptibility to recurrent infection [14, 17–27]. There has been relatively little investigation of the risk factors for RUTIs. The current epidemiologic study, therefore, focused more on identifying host-related risk factors for RUTIs in young women by selecting women with recent and frequent

Table 2. Association of recurrent urinary tract infection (UTI) with selected characteristics.

Variable	University clinic, %		Health maintenance organization, %	
	Case patients (n = 100)	Control subjects (n = 113)	Case patients (n = 129)	Control subjects (n = 140)
Sexual activity				
Sexual intercourse, ever	100	85[a]	100	89[a]
Sexual intercourse, past year	100	78[a]	98	75[a]
Sexual intercourse, ⩾4 times past month	94	47[a]	84	49[a]
New sex partner, past year	64	41[a]	43	24[a]
Age at 1st intercourse, ⩽15 years	16	16	33	15[a]
Lifetime sex partners ⩾5	36	27	50	36[a]
⩾2 Sex partners, past year	32	24	24	14[a]
Contraceptive practices, past year				
Any spermicide use[b]	59	36[a]	52	34[a]
Any spermicide-coated condom use	56	34[a]	50	30[a]
Any oral contraceptive use	70	55[a]	61	42[a]
Any diaphragm/cervical cap use	14	7	5	4
Genitourinary infection history				
Age at first UTI ⩽15 years	22	6[a]	20	9[a]
Kidney infection, ever	13	4[a]	19	6[a]
History of bacterial vaginosis	11	3[a]	26	9[a]
History of STD[c]	16	9	33	26
Chronic disease history[d]	0	0	2	1
Family history				
History of UTI, mother	47	25[a]	46	27[a]
History of UTI, sister	18	15	32	17[a]
Voiding habits, past year				
Infrequent or no precoital voiding[e]	62	53	57	51
Infrequent or no postcoital voiding[e]	33	33	28	26
Daytime frequency of urination, ⩽3 times/day	27	16	26	16
Getting up at night to urinate (usually/always)	8	15	24	16
Delayed voiding	48	51	47	48
Difficulty holding urine, ever	12	6	27	15
Personal hygiene practices, past year				
Wiping back to front after bowel movement	16	17	19	29
Use of hot tub once or more per month	3	8	16	9
Any douching	4	2	22	17
Tampon use	82	81	66	75
Time between changing tampons, ⩾8 h on light days	7	7	6	10
Use of cotton underwear	64	68	69	73
Use of noncotton hose/tights, ⩾4 days a week	6	10	28	15[a]
Beverage consumption, past year				
Daily water consumption, ⩽5 glasses	89	81	84	88
Daily consumption of caffeinated beverages, ⩾3 glasses	18	17	30	31
Daily consumption of cranberry juice, ⩾1 glasses	21	8[a]	16	14
Other				
ABO blood group nonsecretor	20	22	27	20
Body mass index ⩾27.3	2	4	17	20

NOTE. STD, sexually transmitted disease.

[a] $P < .05$ for case patients vs. control subjects.

[b] Includes foam, foam and condoms, diaphragm, cervical cap, spermicide-coated condoms, and sponge.

[c] Includes chlamydia, gonorrhea, syphilis, herpes, trichomonas, genital warts, and pelvic inflammatory disease.

[d] Includes interstitial cystitis, diabetes, and hypertension.

[e] Sexually active women only.

recurrences (multiple infections during the preceding 6–12 months). As with an earlier study of cystitis [1], we were able to evaluate possible associations singly and in multivariate models in 2 study populations, university women and a population-based sample of women HMO enrollees, who are generally representative of the Puget Sound region [28]. The predictors of RUTI that we identified were similar for both groups, providing evidence that the results apply to a broad spectrum of community-dwelling young women.

Our results, noting that sexual and contraceptive exposures associated with sporadic acute UTIs were also associated with RUTIs, indicate that young women experiencing RUTIs are not as distinct from women with sporadic infections as the literature on recurrence might suggest. The strongest univariate associations were with any intercourse (lifetime) and with any intercourse during the past year. These variables had so few unexposed case patients that they could not be reliably evaluated in multivariate models. However, frequency of inter-

Table 3. Factors associated with recurrent urinary tract infection (UTI): multivariate models.

Variable	University clinic	Health maintenance organization	Combined sites[a]
Intercourse in past month[b,c]			
4–8 Times	9.7 (3.3–28.5)	5.0 (2.3–10.9)	5.8 (3.1–10.6)
⩾9 Times	15.7 (6.0–41.6)	9.4 (4.4–20.4)	10.3 (5.8–18.3)
Age at first UTI, ⩽15 years[d]	2.9 (1.0–8.5)	4.9 (1.9–12.4)	3.9 (1.9–8.0)
History of UTI, mother	2.1 (1.0–4.2)	2.6 (1.4–4.9)	2.3 (1.5–3.7)
Any spermicide use, past year	1.8 (0.8–3.7)	1.8 (1.0–3.4)	1.8 (1.1–2.9)
New sex partner, past year	1.3 (0.6–2.7)	2.8 (1.4–5.6)	1.9 (1.2–3.2)

NOTE. Data are odds ratio (95% confidence interval).
[a] Includes site as covariate in model.
[b] Past month, 1 month before most recent UTI.
[c] Referent is intercourse 0–3 times, past month.
[d] Referent is all other women.

course during the month before the reference date was strongly associated with case status when included in multivariate models. We also observed an ~2-fold increased risk of RUTIs among women reporting spermicide exposure during the 1 year preceding the reference date. These associations have been documented in studies of sporadic acute infection [1–7, 29]. With ongoing exposure, these factors are plausibly associated with an increased risk for RUTIs as well. Both intercourse and spermicide exposure increase periurethral *Escherichia coli* colonization [30–32], and such colonization occurs more frequently and for prolonged periods in women with RUTI [22, 32, 33].

Of interest with regard to host factors predictive of RUTIs were our observations regarding a reported history of UTIs in the mother and a history of early UTI onset in the woman herself. These variables were associated with 2–4-fold increases in risk of recurrence in both study groups and were the most strongly associated variables after recent frequency of sexual intercourse. For both sites, these factors were more strongly associated with RUTIs in our more highly recurrent case group. Both maternal history and childhood onset of cystitis suggest that inherited factors may be important in some women with recurrent infections, especially those with onset before first sexual intercourse and possible spermicide exposure. Alternatively, these observations could reflect other shared environmental factors or behaviors present in both mothers and daughters. In either case, these findings are supported by studies of the long-term natural history of recurrent bacteriuria and symptomatic UTIs in childhood [34, 35]. Kunin's [34] follow-up study of schoolgirls found that girls who experienced these infections during childhood were more prone to bacteriuria and symptomatic infections as adults.

Other studies, such as those associating specific blood group antigens or nonsecretor phenotype, also support an association between genetic factors and history of RUTIs or pyelonephritis [14, 17, 21–24, 26, 33]. Although we evaluated ABO, P1, Lewis, and nonsecretor blood group phenotypes, they were not risk factors for recurrent infection in this study group. However, the studies that associated nonsecretor status with this outcome were conducted in study groups quite different from ours, namely in selected populations of older women or in women referred for urologic evaluation. Thus, nonsecretor status may not figure prominently in the recurrent infections experienced by our younger, primary care–based study population, in whom sexual and contraceptive practices continued to be the most important risk factors. Of interest, when we examined a subgroup of women from the HMO who were at decreased risk for other factors (i.e., women who were ⩾26–30 years old, married, and without spermicide exposure), nonsecretor phenotype approached significance (OR, 3.6; 95% CI, 0.8–16.4). It seems likely that women experiencing RUTIs are not a homogeneous group and that the factors associated with recurrence may differ by age and other population characteristics. In younger women, the behavioral factors implicated in sporadic UTIs are likely to continue to predominate in RUTIs. In older populations, the role of sexual and contraceptive practices may be diminished, and other factors (e.g., nonsecretor status) may become relatively more important. This possibility requires further study.

Our data have several limitations. Our case group comprised women who had experienced RUTIs over the preceding 6–12 months. Because our inquiry focused on factors that were associated with this case definition, the principal time frame of interest was the 1-year period before the most recent episode. It is possible that some of our behavioral exposures of interest could have been modified by case patients in response to the occurrence of repeated infections during (or preceding) that time. This may be particularly true for behaviors that are established risk factors for sporadic infection or that have received attention in the popular press—primarily sexual intercourse, spermicide exposure, cranberry juice (or other fluid) consumption, or voiding behaviors. In this event, our risk estimates would be biased toward the null. Recall of past behaviors is also more subject to bias in a case-control study design. Thus, while any versus no sexual activity could be collected for the 12-month period of interest, the frequency of intercourse could only be reliably ascertained for the more recent time frame (the month before the most recent episode). In our model, frequency of intercourse thus describes the risk associated with the most recent UTI recurrence, whereas the other variables in the model refer to risks over longer time frames (12 months or lifetime).

From the standpoint of prevention of RUTIs, our final set of predictors did not include some of the more modifiable behaviors and practices that we assessed (e.g., voiding after intercourse or increased fluid intake). However, the potentially modifiable behaviors of sexual frequency and spermicide use were important contributors to an increased risk of UTI in our recurrent case group. Because it appears that spermicide exposure is increasingly due to the use of spermicide-coated male condoms, it may be reasonable to counsel women with RUTIs to avoid condoms with these lubricants [36]. Among women

with onset of infection in childhood or whose mothers also experienced UTIs, host genetic factors may play a role in susceptibility to recurrence. These factors, when more fully evaluated, are likely to provide new avenues for counseling and intervention.

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