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Risk Factors for Second Urinary Tract Infection among College Women

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To better understand the etiology of recurrent urinary tract infection (UTI), the authors followed a cohort of 285 female college students with first UTI for 6 months or until second UTI. A first UTI due to *Escherichia coli* was followed by a second UTI three times more often than was a non-*E. coli* first UTI (24 vs. 8%; $p = 0.02$). In a logistic regression analysis limited to the 224 women from the University of Michigan Health Service and the University of Texas at Austin Health Service from September 1992 to December 1994, with a first UTI due to *E. coli*, vaginal intercourse increased the risk of a second UTI with both a different (odds ratio (OR) = 1.60, 95% confidence interval (CI): 1.19, 2.15) and the same (OR = 1.37, 95% CI: 0.91, 2.07) uropathogen, as did using a diaphragm, cervical cap, and/or spermicide (same uropathogen: OR = 1.53, 95% CI: 0.95, 2.47; different uropathogen: OR = 1.77, 95% CI: 1.22, 2.58). Condom use decreased the risk of a second UTI caused by a different uropathogen (OR = 0.68, 95% CI: 0.48, 0.99) but had no effect on a second UTI caused by the same *E. coli* (OR = 0.99; 95% CI: 0.66, 1.50). Type or duration of treatment was not associated with a second UTI. Although the risk of second UTI is strongly influenced by sexual behavior, women with a first UTI caused by *E. coli* are more likely than are those with a non-*E. coli* first UTI to have a second UTI within 6 months. *Am J Epidemiol* 2000;151:1194–1205.

Escherichia coli; recurrence; risk factors; sex behavior; urinary tract infections; women

Each year, approximately 7.3 million women visit a clinician for urinary tract infections (UTI) (National Center for Health Statistics, unpublished data, 1995). Half of all women will have at least one UTI by age 30 years (1), an estimated 20–30 percent of women with a first UTI will have two or more episodes (2), and 5 percent will have chronic recurring infections (3). The relative roles of host and bacterial factors on risk of second or repeated UTI are not well understood.

Most studies of UTI pathogenesis include women with culture-confirmed, symptomatic infections regardless of the number of prior UTI. History of prior UTI is a strong predictor of acquiring subsequent infection (4, 5): the 6-month risk of second UTI is an order of magnitude greater than the risk of UTI in the general population (2). One third (5) to one half of recurring UTI are due to the previous infecting organism (6), making it difficult to separate risk factors for acquiring new uropathogens (that lead to symptoms) from risk factors for developing symptoms from an existing colonization. Although the number of prior UTI can be adjusted for in the analysis, statistical adjustment summarizes overall categories of other variables, potentially obscuring important effects. For example, a risk factor for colonization with a uropathogen—a crucial first step that might be subject to intervention—may have little or no effect on risk of recurrent symptomatic infection. The effects of this factor would remain undetected if first UTI were not examined separately.

Combining first and subsequent UTI is especially problematic when addressing bacterial virulence factors. A bacterial virulence factor may be associated with risk of first UTI but be associated with decreased risk of second or multiple UTI (6). Virulence factors leading to first UTI may protect against second UTI by stimulating host response to those factors, or chronic, recurring infection due to the same bacteria may signal a failure in host response. One third of the women with community-acquired *Escherichia coli* UTI have subsequent UTI caused by the same strain (5). Among women with recurring UTI, 68 percent may have a recurrence caused by the same strain (7).

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Abbreviations: CI, confidence interval; OR, odds ratio; RR, rate ratio; UTI, urinary tract infection.

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To understand better the pathogenesis of UTI, we followed a cohort of 285 women with first UTI for 6 months or until the second UTI. This standardized prior history of UTI and allowed us to determine whether the behavioral factors for the first and second UTI were the same. Moreover, we were able to estimate the risk of second UTI associated with first infection due to a particular uropathogen. We have previously reported the retrospectively determined patterns of first UTI (8, 9) and have described the frequency of *E. coli* virulence characteristics (6, 10) among *E. coli* isolated from this cohort.

MATERIALS AND METHODS

Study protocol

Study participants were recruited at the University of Michigan Health Service and the University of Texas at Austin Health Service from September 1992 through December 1994. At the University of Michigan, enrollment was offered to all female students referred to the University of Michigan Laboratory for urinalysis who had one or more urinary symptoms (frequency, urgency, dysuria, hematuria, nocturia, fever, or back or flank pain), had no UTI history, were aged 18–39 years, and stated that they intended to stay in the same geographic area over the next 6 months. At the University of Texas, female students aged 18–39 years who intended to stay in the same geographic area over the next 6 months and who had clinically diagnosed UTI and no history of UTI were referred to a research nurse for further eligibility screening and an invitation to enroll in the study. At both sites, all consenting women with a urine culture positive for a uropathogen who had a clinical diagnosis of UTI (but not pyelonephritis) who were not currently pregnant, married, diabetic, or recently catheterized were accepted into the study. Treatment of the UTI was decided by the patient's clinician. Participants were asked to return for a follow-up urine culture after completion of their medication.

Laboratory personnel at both sites actively monitored all incoming urine specimens for potential second UTI among study participants. Medical records were reviewed at the time of enrollment to confirm eligibility and obtain the treatment prescribed; records were reviewed again at the end of the follow-up period to check for missed recurrences. We also ascertained recurrence by self-report of clinician diagnosis.

At the University of Michigan, a study representative screened for eligibility 1,342 women referred for urinalysis. We eliminated 827 (62 percent) because they had a history of UTI, were pregnant, were older than age 39 years, were not available for follow-up, or refused to hear more about the study (n = 211). The most common reason for refusal was "too busy." After screening, the remaining 515 potentially eligible women were offered enrollment, and 304 (59 percent) consented. Those who refused were similar to those who consented with respect to age and racial group. Of those who consented, 141 (46 percent) had a positive urine culture, one or more UTI symptoms, clinician diagnosis of UTI, and no history of UTI or other exclusionary criteria noted in their medical record. The major reason for exclusion was a negative urine culture. At the University of Texas, potentially eligible cases were referred to the study nurse by their clinician. The tracking of referrals was unreliable, so we have no good estimate of the consent rate. Nevertheless, the study nurse reported that most women who met with her participated. Of the 172 potential cases enrolled at the University of Texas, 16 were ineligible because they were married, one was not a student, and 11 had missing data for one or more eligibility criteria, leaving 144 cases (84 percent).

Measuring Instruments

Study participants completed a self-administered questionnaire at enrollment and 2, 4, and 6 months after enrollment and/or at the time of recurrence. The questionnaire asked about sociodemographic variables; medical and sexual histories; and sexual behavior, birth control methods, and diet during the previous 2 weeks. This time period was chosen both because recent exposures are most pertinent for UTI risk and to minimize problems of recall. Questionnaires were mailed 1 week before the due date; participants were telephoned 1 week after the follow-up due date to remind them and/or to complete the questionnaire by telephone.

Sample collection

Clean-voided urine specimens were obtained from potential study participants at time of UTI diagnosis and were cultured and identified as described previously (6).

Definitions

A UTI was defined as a clinically diagnosed UTI, with one or more urinary symptoms and 1,000 or more cfu/ml urine of a known uropathogen, consistent with published guidelines for diagnosis of acute uncomplicated cystitis in clinical trials (11). Women with a clinical diagnosis of pyelonephritis were excluded. A woman was considered to have a first UTI if she reported no history of a previous UTI and no history of

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a previous UTI was documented in her university medical record. We considered the woman cured if a urine culture after completion of antimicrobial therapy and resolution of symptoms had no growth or symptoms resolved and the urine culture yielded a genotypically different *E. coli* than that which caused the first UTI (based on DNA hybridization if both isolates were *E. coli*). If a woman had a positive urine culture (≥1,000 cfu/ml urine of a known uropathogen) at follow-up, she was asked to return for an additional urine culture. Treatment after a positive follow-up culture was left to the discretion of her treating clinician.

Because a follow-up culture after the first UTI and culture results for the second UTI were not always available, we used two alternative definitions for second UTI. In conjunction with a clinician diagnosis, a second UTI was defined as 1) urinary symptoms with a urine culture positive for any known uropathogen after a negative follow-up culture or a symptomatic infection with a genotypically different organism without a negative follow-up culture. These are designated "culture-confirmed symptomatic episodes" (n = 40); or 2) urinary symptoms after initial UTI. These are designated as "symptomatic episodes" (n = 53). Symptomatic episodes include all culture-confirmed symptomatic episodes.

Bacterial strains, plasmids, and labeling DNA probes

E. coli strains used as controls for hybridization studies, the plasmids used as sources, and genes and fragment size used as probes were described previously (6, 10). All genes were originally isolated from *E. coli*. Since the *pap* gene probe can strongly hybridize to both *pap* and *prs* genes, we use the system of Blum et al. (12) and call pap-hybridizing sequences *prf* for P-related fimbriae. Similarly, as pIL14 hybridizes to AFAI-IV and F1845 pili, we call sequences hybridizing this probe *drb*, for Dr-binding adhesins. We determined Dr subtypes as previously described (13). The *kps*MT gene probe is specific to group II *E. coli* capsule genes and does not hybridize to strains containing either group I or group III capsule genes (14). Preparation of DNA for use as probes has been described previously (6, 10).

Total DNA isolation, dot blots, and Southern blots

We performed crude DNA isolations for dot blots as described previously (6, 10). For Southern blots, larger amounts of purified total DNA were prepared, and the DNA was digested and transferred as described previously (6, 10). We performed dot blots in duplicate for each probe, and films were read independently by two readers. Blots that were questionable on both films were retested (6, 10). Each *E. coli* strain was assigned a nine-digit binary code in which each digit corresponded to the presence or absence of a virulence characteristic. We refer to these dot blot hybridization patterns as signatures. Signatures do not identify clonal groupings (10). When first and second *E. coli* isolates from one individual have the same signature, they have so far always had identical pulsed-field gel electrophoresis patterns (6); thus, for the analysis in this paper, we considered *E. coli* from second UTI with the same signature as the first UTI to be the same strain.

Data entry and statistical analysis

All data were coded and entered twice by different individuals. The files were compared, and descrepancies were checked against the original questionnaire for accuracy.

Each participant had baseline information (e.g., race, virulence characteristics of first UTI isolate) and up to three follow-up records, one for each 2-month interval describing their behavior during the 2 weeks prior to completing the questionnaire. Information from all questionnaires prior to recurrence or until the end of follow-up were included in the analysis. Participants with a second UTI in the first or second interval had only one or two follow-up records, respectively, because participation was terminated after a second UTI. Recurrence information was linked to the appropriate questionnaire data for each 2-month interval after enrollment. We calculated the rate of second UTI as the number of UTI per person-months exposed.

Associations between exposure variables and the rate of second UTI were very similar regardless of whether we used culture-confirmed symptomatic or all symptomatic episodes. We present the results using all symptomatic episodes as the outcome, but numbers of culture-confirmed, symptomatic episodes are included in the tables for comparison.

We describe associations between exposures and rate of second UTI with rate ratios and their approximate 95 percent confidence intervals (15). We tested differences between groups for categorical variables with chi-square tests and for continuous variables with Student's t tests with a significance level of $\alpha = 0.05$. We stratified all sexually related behaviors by frequency of vaginal intercourse and calculated Mantel-Haenszel summary rate ratios and approximate 95 percent confidence intervals using dEPID (16).

We examined the effects of multiple concurrent variables on the rate of second UTI after first UTI caused by *E. coli* by using three different outcomes: 1) all second UTI together; 2) second UTI caused by the same *E. coli*; and 3) second UTI caused by a different

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uropathogen. For each outcome, we performed discrete-time survival analyses with 2-month intervals using logistic regression (17). The model for all second UTI included frequency of vaginal intercourse, condom and other birth control method use during the 2 weeks prior to the questionnaire, an indicator of whether no birth control method was used, time since first engaged in sexual activity with the current sex partner (partnership <4 months, 4 to <8 months, 8 to <12 months, and a year or more), and an indicator for months 3–4 and 5–6 since first UTI (to model changes in risk over time). Oral contraceptives were the referent group for birth control method because the numbers of women using no method were small. Cutpoints for time engaged in sexual activity with the current sex partner were determined by using quartiles of the distribution (considering data from all 2-month intervals together) and then rounding each quartile to the nearest month for ease of interpretation. A subset of these variables was used for the other two models. We used the $\log(x + 1)$ transformation of the variables measuring frequency during the previous 2 weeks of vaginal intercourse, condom use, and all other birth control methods. The $\log(x + 1)$ transformation improved the fit of the model over a linear relation for all three variables. Other variables were added individually to the base model. We compared the effect of each individual *E. coli* virulence factor with that of *E. coli* containing only type I pili by using two dummy variables: an indicator of the presence of the bacterial virulence factor of interest and an indicator for the presence of all other non-type I factors. If a woman was infected with two different *E. coli*, one was chosen at random for inclusion in this analysis. Women infected with an *E. coli* and a non-*E. coli* were considered to have *E. coli* UTI. All adjusted analyses were performed using SAS for Windows 6.10 (18).

RESULTS

Study population characteristics

We enrolled 285 eligible women with first UTI; 263 (92 percent) completed at least one follow-up questionnaire, and 211 (74 percent) were followed for 6 months or until their second UTI. There were 53 symptomatic second UTI, of which 40 were confirmed by culture. Six symptomatic second UTI were identified by self-report of clinician diagnosis only. The majority (85 percent) of first UTI were caused by *E. coli*, and the remainder by *Staphylococcus saprophyticus* (5 percent), *Proteus* (3 percent), and *Klebsiella* (3 percent), with *Enterobacter*, *Citrobacter*, Group B *streptococcus*, and other staphylococcal species making up the remainder. Although we defined a UTI as 1,000 or more cfu/ml urine of a single uropathogen in the presence of one or more urinary symptoms, 76 percent of women had 100,000 or more cfu/ml. The majority (86 percent) of second UTI were also caused by *E. coli* and the remainder by *S. saprophyticus* (7 percent), *Proteus* (5 percent), and *Klebsiella* (2 percent).

When compared by site of enrollment, study participants did not differ with respect to rate of second UTI, frequency of vaginal intercourse, condom use, or length of relation. However, more participants from Michigan than from Texas were Black (15 vs. 5 percent), and fewer were Hispanic (2 vs. 11 percent) ($p = 0.001$). As behavioral variables did not differ within racial groups across sites, all participants were combined for presentation.

The most common first UTI symptoms reported by women with *E. coli* compared with all other uropathogens were frequency (93 and 95 percent), urgency (92 and 83 percent), dysuria (88 and 88 percent), suprapubic pressure (72 and 66 percent), nocturia (57 and 60 percent), and gross hematuria (51 and 39 percent), respectively. Back pain (28 and 31 percent), flank pain (16 and 17 percent), fever (19 and 12 percent), and chills (24 and 5 percent) were less common in both groups. Only five women (2 percent) had an objectively measured temperature greater than 99.9° F.

Treatment was decided by the treating clinician. The majority (63 percent) were treated with trimethoprim-sulfa for 1–15 days. Twenty-six percent were treated with nitrofurantoin for 3–14 days, and the remainder were treated with some other antimicrobial. Ten percent were treated with trimethoprim-sulfa for 1 or 2 days. Choice of

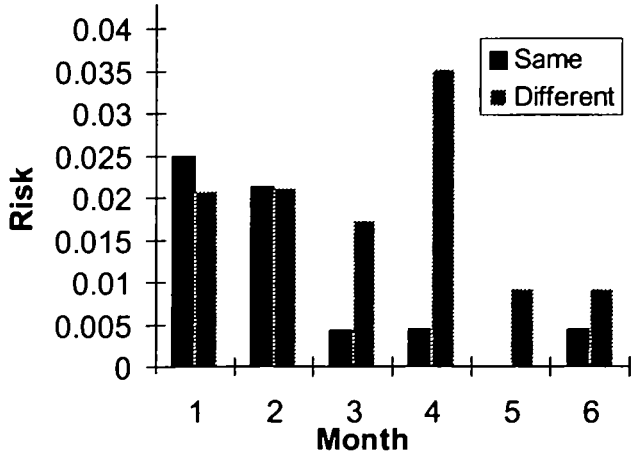


FIGURE 1. Monthly incidence of second UTI among women from the University of Michigan Health Science Service and the University of Texas at Austin Health Science Service from September 1992 to December 1994 with first UTI due to *E. coli* by whether recurrence was with the same or a different bacteria ($n = 224$ women). The average standard error for recurrence with the same bacteria was 0.0054; for recurrence with a different bacteria, it was 0.0087.

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TABLE 1. Rate of second urinary tract infection (UTI) by age at enrollment and race and sexual behavior reported bimonthly between first and second UTIs in 224 college women with first UTI caused by *Escherichia coli* (total person-months of exposure = 1,140), University of Michigan Health Service and University of Texas at Austin Health Service, 1992–1994*

Characteristic	Person-months of exposure	No. with second UTI		Rate of second UTI (all symptomatic episodes) per 100 person-months	RR†	95% CI†
		Culture-confirmed symptomatic episodes	All symptomatic episodes			
Age (years)						
18–19	262	2	6	2.29	1.00	
20–21	448	21	25	5.58	2.44	1.00, 5.94
22–23	280	8	12	4.29	1.87	0.70, 4.99
24–39	150	9	10	6.67	2.91	1.06, 8.01
Race						
White	850	29	36	4.24	1.00	
Black	88	1	2	2.27	0.54	0.13, 2.23
Other	202	10	15	7.43	1.75	0.96, 3.20
Lifetime no. of sex partners						
1	252	9	15	5.95	1.00	
2–3	402	16	19	4.73	0.79	0.40, 1.56
4–7	304	9	12	3.95	0.39	0.31, 1.42
≥8	174	6	7	4.02	0.68	0.28, 1.66
Vaginal intercourse in previous 2 weeks						
None	312	4	6	1.92	1.00	
1–5	522	16	21	4.02	2.09	0.84, 5.18
≥6	304	20	26	8.55	4.45	1.83, 10.81
Digital stimulation in previous 2 weeks						
0–1	336	7	9	2.68	1.00	
2–7	588	20	27	4.59	0.92	0.34, 2.50
≥8	212	13	17	8.02	0.95	0.21, 4.25

Table continues

treatment regimen was very similar for women with non-*E. coli* and *E. coli* UTI, with most treated with trimethoprim-sulfa (69 percent non-*E. coli* vs. 62 percent *E. coli*; $p = 0.56$). The average duration of treatment did not differ by infecting bacteria ($p = 0.69$).

Risk of second UTI by initial infecting organism

Among the 224 women with first UTI caused by *E. coli* who completed at least one follow-up, 53 (24 percent) had a symptomatic episode, and 42 (19 percent) had a culture-confirmed symptomatic episode after culture-confirmed cure within 6 months. Thirty-nine women with non-*E. coli* first UTI completed at least one follow-up; three (8 percent) had a symptomatic episode, and two (5 percent) had a culture-confirmed symptomatic episode after a negative follow-up urine culture within 6 months. Risk of a second symptomatic UTI was significantly higher among women whose first UTI was caused by *E. coli* (53 of 224 vs. three of 39, $p = 0.02$). When the analysis was limited to the 27 women with non-*E. coli* UTI and 137 women with *E. coli* UTI who were treated with trimethoprim-sulfa, women with non-*E. coli* UTI still had a second infection at significantly lower rates (two of 27 vs. 34 of 137, $p = 0.045$).

For women with first UTI caused by *E. coli*, risk of a second UTI within 6 months was 25 percent among women treated with trimethoprim-sulfa (34 of 137) or nitofurantoin (15 of 61) and 14 percent (three of 22) among those treated with other regimens (14 percent), but the differences between the three groups were not statistically significant (chi-square $p = 0.51$) (treatment was unknown for four individuals). The rates of second UTI after non-*E. coli* first UTI were similar by treatment: 7 percent (two of 27) for trimethoprim-

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TABLE 1. Continued

Characteristic	Person-months of exposure	No. with second UTI		Rate of second UTI (all symptomatic episodes) per 100 person-months	RR	95% CI
		Culture-confirmed symptomatic episodes	All symptomatic episodes			
Receptive oral sex in previous 2 weeks‡						
None	608	14	22	3.62	1.00	
1–2	334	18	21	6.29	1.20	0.64, 2.26
≥3	192	8	10	5.21	0.73	0.31, 1.69
Length of current partnership (months)‡						
≥12	306	9	15	4.90	1.00	
No current partner	212	2	4	1.89	0.42	0.23, 7.89
<4	242	15	17	7.02	1.57	0.79, 3.10
4 to <8	242	11	13	5.37	0.98	0.48, 2.00
8 to <12	136	3	4	2.94	0.57	0.21, 1.54
New sex partner since enrollment‡						
No	992	32	10	1.01	1.00	
Yes	146	8	43	29.45	1.65	0.83, 3.30
Birth control method‡,§						
Oral contraceptives	436	16	22	5.05	1.00	
None	202	1	2	0.99	0.20	0.05, 0.83¶
Condoms	242	9	13	5.37	1.12	0.55, 2.29
Oral contraceptives and condoms	194	7	8	4.12	0.89	0.39, 2.01
Diaphragm or cap (alone or with any other method)	20	4	5	25.00	3.56	1.32, 9.60
Spermicide without condoms (includes other methods or alone)	18	2	2	11.11	2.40	0.55, 10.44
Some other method	8	0	0	0.00		

* Rate ratios and 95% confidence intervals for other sexual behaviors and birth control method are adjusted for frequency of vaginal intercourse. Person-months may not total 1,140 because of missing exposure information. Exposure information was missing for no more than 2% for any one variable.

† RR, rate ratio; CI, confidence interval.

‡ Mantel-Haenszel rate ratio adjusted for frequency of vaginal intercourse. Missing data for 2 person-months on frequency of vaginal intercourse.

§ Mutually exclusive categories.

¶ Crude RR, since there were no cases of second UTI in two of three strata.

sulfa and 10 percent (one of 10) for nitofurantoin (chi-square $p = 0.88$). We observed no recurrences among the two women with first UTI caused by non-*E. coli* who were treated with some other regimen. Average duration of treatment was not associated with recurrence for *E. coli* or non-*E. coli* UTI ($p = 0.3$).

Age, race, length of relationship, condom use, and frequency of engaging in oral sex or digital stimulation were similar among women with first UTI caused by *E. coli* and those whose first UTI was caused by some other uropathogen (data not shown). However, women with first UTI caused by *E. coli* were significantly more likely than were those with non-*E. coli* first UTI to have engaged in vaginal intercourse during the 2 weeks prior to their first UTI (96 vs. 86 percent, $p = 0.03$). Because of the small number of second UTI among women infected with non-*E. coli*, the remainder of the analyses are limited to women with first UTI caused by *E. coli*.

Second UTI caused by a different uropathogen occurred twice as frequently as recurrence with the same *E. coli* (16 vs. 8 percent). Second UTI caused by a genetically different *E. coli* or other uropathogen were spread fairly evenly throughout the follow-up period; by contrast, most (89 percent) of second UTI caused by the identical *E. coli* occurred within the 3

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months after first UTI (figure 1). Patterns were similar for culture-confirmed and symptomatic episodes.

Host characteristics and behaviors

Rate of second UTI was lowest among those aged 18–19 years and was fairly constant in the older age groups (table 1). We observed few second UTI among Black participants. The highest rate of second UTI was among women who self-identified as "other" race, but the numbers are small and the differences are not statistically significant.

Women who reported a history of eight or more lifetime sex partners had a lower rate of second UTI, but the differences were not statistically significant (table 1). Recent and more frequent sexual activity increased the rate of second UTI. Oral contraceptives were the most popular birth control method, although they were often used with condoms, spermicides, condoms and spermicides, or a diaphragm or cervical cap. However, only women who used diaphragms or cervical caps had a significantly higher incidence of second UTI than did women who used oral contraceptives. Women who used no contraceptive method had the lowest risk.

We examined the associations of several health behaviors with rate of second UTI. Regularly drinking cranberry juice was associated with a slightly, but not significantly, lower rate of second UTI (rate ratio (RR) = 0.78, 95 percent confidence interval (CI): 0.42, 1.44) (data not shown). Women who regularly took vitamin C compared with those who did not were equally likely to have a second UTI (RR = 1.18, 95 percent CI: 0.64, 2.19). More frequent consumption of carbonated beverages was associated with significantly lower rates of second UTI (daily vs. never, RR = 0.33, 95 percent CI: 0.12, 0.90). The type of menstrual protection used did not appear to be associated with rate of second UTI. There was no clear pattern with voiding habits, and the associations are not statistically significant. Only women who reported wiping in either direction after urination had an increased rate of second UTI (RR = 1.76, 95 percent CI: 0.91, 3.43); wiping back-to-front as opposed to front-to-back had no impact on the rate of second UTI (RR = 0.91, 95 percent CI: 0.45, 1.85). There was no association with cigarette use (RR = 1.08, 95 percent CI: 0.59, 1.99). However, women who reported taking antibiotics during the 2 weeks prior to the follow-up survey had a higher rate of second UTI (RR = 1.75, 95 percent CI: 0.94, 3.27).

Bacterial virulence characteristics

We probed all *E. coli* isolates for the presence of nine different virulence characteristics either known or hypothesized to be associated with risk of acquiring UTI. Results of a preliminary analysis of this set has been presented previously (6). None of the virulence characteristics individually or in the most commonly occurring groups of virulence factors were associated with increased risk of second UTI, although several factors seemed protective (data not shown).

Second UTI caused by the same versus a different uropathogen

To explore the factors associated with a second UTI caused by the same or a different uropathogen, we analyzed the data by using two additional outcomes: second UTI caused by the same *E. coli* (n = 18) and second UTI caused by a different uropathogen (n = 35). In both of these analyses, the most important factor was frequency of vaginal intercourse (table 2). Having a new sex partner was associated with increased rate of second UTI with the same *E. coli* but not a different uropathogen. Diaphragm use increased the risk of a second UTI with either the same *E. coli* or a different uropathogen. Wiping in either direction after urination was associated with recurrence with a different uropathogen, but not with the same *E. coli*.

The effects of bacterial characteristics on risk of second UTI with the same or a different uropathogen are difficult to interpret because of small sample sizes (data not shown). Compared with the overall risk of second UTI with the same *E. coli*, the point estimates for the presence of P pili (RR = 0.44, 95 percent CI: 0.15, 1.29), cytotoxic necrotizing factor I (RR = 0.43, 95 percent CI: 0.10, 1.78), hemolysin (RR = 0.44, 95 percent CI: 0.13, 1.44), and S fimbrial adhesin (RR = 0.61, 95 percent CI: 0.19, 1.98) in the initial isolate are negatively associated with risk of a second UTI, but the confidence intervals are wide. None of these factors were associated with risk of second UTI caused by a different uropathogen (P pili, RR = 0.97, 95 percent CI: 0.58, 1.68; cytotoxic necrotizing factor I, RR = 1.03, 95 percent CI: 0.55, 1.96; hemolysin, RR = 0.81, 95 percent CI: 0.43, 1.51; S fimbrial adhesin, RR = 0.91, 95 percent CI: 0.47, 1.79). Presence of one Dr subtype, AFAV, in the initial isolate, was positively associated with second UTI caused by the same *E. coli* (RR = 2.10, 95 percent CI: 0.70, 6.33) but was negatively associated with a second UTI caused by a different uropathogen (RR = 0.45, 95 percent CI: 0.07, 3.05), and neither result was statistically significant.

Multivariate analyses

We included frequency of vaginal intercourse, diaphragm use, cervical cap or spermicide use, condom use, and starting a new sexual partnership since

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TABLE 2. Rate of second urinary tract infection (UTI) with the same or a different uropathogen than the *Escherichia coli* that caused the first UTI, by selected behavioral variables in 224 college women with first UTI caused by *E. coli* (total person-months of exposure = 1,140), University of Michigan Health Service and University of Texas at Austin Health Service, 1992–1994*

Characteristic	Person-months of exposure	Rate with second UTI due to the same *E. coli* (per 100 person-months)	RR†	95% CI†	Rate with second UTI due to a different uropathogen (per 100 person-months)	RR	95% CI
Vaginal intercourse in previous 2 weeks							
None	312	0.64	1.00		1.28	1.00	
1–5	522	1.72	2.69	0.58, 12.45	2.30	1.79	0.58, 5.56
≥6	304	2.30	3.59	0.75, 17.29	6.25	4.88	1.66, 14.33
Lifetime no. of sex partners‡							
1	252	1.59	1.00		4.37	1.00	
2–3	402	1.74	1.10	0.32, 3.74	2.99	0.68	0.30, 1.55
4–7	304	1.97	1.24	0.35, 4.40	1.97	0.45	0.17, 1.22
≥8	174	0.57	0.36	0.04, 3.23	3.45	0.79	0.29, 2.13
New sex partner since enrollment‡							
No	994	1.21	1.00		3.12	1.00	
Yes	146	4.11	3.40	1.28, 9.07	2.74	0.88	0.31, 2.49
Birth control method§							
Oral contraceptives	436	1.61	1.00		3.44	1.00	
None	202	0.50	0.31	0.04, 2.51	0.50	0.14	0.02, 1.09
Condoms	242	2.89	1.80	0.63, 5.13	2.48	0.72	0.28, 1.86
Oral contraceptives and condoms	194	1.03	0.64	0.13, 3.09	3.09	0.90	0.35, 2.32
Diaphragm or cap (alone or with any other method)	20	5.00	3.11	0.38, 25.31	20.00	5.81	1.93, 17.52
Spermicide without condoms (includes other methods or alone)	18	0.00			11.11	3.23	0.74, 14.12
Some other method	8	0.00			0.00		
Wipe after urination							
Front to back	614	1.63	1.00		2.61	1.00	
Back to front	284	1.41	0.86	0.27, 2.76	2.46	0.95	0.39, 2.30
Either direction	174	1.72	1.06	0.29, 3.85	5.75	2.21	1.00, 4.86
Other	62	1.61	0.99	0.13, 7.73	1.61	0.62	0.08, 4.67
Antibiotic use in previous 2 weeks							
No	892	1.12	1.00		2.58	1.00	
Yes	216	2.31	2.06	0.71, 6.04	4.17	1.62	0.75, 3.49

* Person-months may not total to 1,140 because of missing exposure information. Exposure information was missing for no more than 3% for any one variable.
† RR, rate ratio; CI, confidence interval.
‡ One woman reported no sex partners.
§ Mutually exclusive categories.

first UTI as independent variables in two discrete-time survival models, one with recurrence caused by the same *E. coli* as the dependent variable and the other with recurrence caused by a different uropathogen as the dependent variable (see Materials and Methods). After adjustment for other variables, the results are similar to that found in the bivariate analysis. Engaging in one act of vaginal intercourse versus none in the previous 2 weeks was positively associated with recurrence with both a different (odds ratio (OR) = 1.60, 95 percent CI: 1.19, 2.15) and the same (OR = 1.37, 95 percent CI: 0.91, 2.07) uropathogen, as was

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TABLE 3. Time-dependent logistic regression model predicting risk of second urinary tract infection (UTI) in 224 college women with first UTI caused by *Escherichia coli* (total person-months of exposure = 1,140), University of Michigan Health Service and University of Texas at Austin Health Service, 1992–1994*

Variable	Coefficient	SE†	*p* value	OR†	95% CI†
Vaginal intercourse (1 time vs. none)‡	0.5742	0.2387	0.02	1.49	1.08, 2.06
Vaginal intercourse with a condom (1 time vs. none)‡	−0.4279	0.2189	0.05	0.74	0.55, 1.00
Vaginal intercourse with diaphragm, cervical cap, or spermicide (1 time vs. none)‡	0.8148	0.2536	0.00	1.76	1.25, 2.48
No birth control method	−1.4005	0.7775	0.07	0.25	0.05, 1.13
Length of current relationship (vs. ≥12 months)					
No current sex partner	0.2424	0.7091	0.73	1.27	0.32, 5.12
Sex partner <4 months	0.4369	0.4115	0.29	1.55	0.69, 3.47
Sex partner 4 to <12 months	−0.1160	0.4086	0.78	0.89	0.40, 1.98
Sex partner 8 to <12 months	−0.7672	0.5994	0.20	0.46	0.14, 1.50
Month 4 (compared with month 2)	−0.4518	0.3586	0.21	0.64	0.32, 1.29
Month 6 (compared with month 2)	−0.6250	0.3989	0.12	0.54	0.24, 1.17
Factors added one at a time to the base model					
Site of recruitment	−0.0793	0.1053	0.45	0.92	0.75, 1.14
New sex partner	0.5662	0.6728	0.40	1.76	0.47, 6.59
Cranberry juice	−0.2799	0.3493	0.42	0.76	0.38, 1.50
Vitamin C	0.1979	0.3484	0.57	1.22	0.62, 2.41
No. of carbonated beverages in previous 2 weeks (vs. none)					
1–3	−0.5857	0.5814	0.31	0.56	0.18, 1.74
4–7	−0.4786	0.5403	0.38	0.62	0.21, 1.79
8–10	−1.3966	0.6886	0.04	0.25	0.06, 0.95
Daily	−1.4429	0.5741	0.01	0.24	0.08, 0.73
Napkin only (vs. tampon only)	0.2412	0.4452	0.59	1.27	0.53, 3.05
Tampon and napkin (vs. tampon only)	0.2577	0.3532	0.47	1.29	0.65, 2.59
Deodorant menstrual protection	−0.3916	0.4348	0.37	0.68	0.29, 1.59
Voiding habits (times/day) vs. 4 times per day					
<4	−0.8488	0.4940	0.09	0.43	0.16, 1.13
5–6	−0.5973	0.3816	0.12	0.55	0.26, 1.16
≥7	−0.6689	0.4781	0.16	0.51	0.20, 1.31

Table continues

using a diaphragm, cervical cap, or spermicide (same uropathogen: OR = 1.53, 95 percent CI: 0.95, 2.47; different uropathogen: OR = 1.77, 95 percent CI: 1.22, 2.58) (data not shown). Having a new sex partner in the previous 2 weeks was positively associated with a second UTI caused by the same *E. coli* (OR = 3.60, 95 percent CI:1.28, 10.09) but not with a different uropathogen (OR = 0.82, 95 percent CI: 0.27, 2.49). Condom use protected against recurrence caused by a different uropathogen (OR = 0.68, 95 percent CI: 0.48, 0.99) but had no association with a second UTI caused the same *E. coli* (OR = 0.99, 95 percent CI: 0.66, 1.50).

We also fit a discrete-time survival model that considered all symptomatic second UTI as the outcome (table 3). After adjustment for the presence of other variables (see Materials and Methods), a single sex act during the previous 2 weeks increased risk of a second UTI by 49 percent (OR = 1.49, 95 percent CI: 1.08, 2.06). Vaginal intercourse with a condom modestly decreased risk of a second UTI (OR = 0.74, 95 percent CI: 0.55, 1.00), and vaginal intercourse with a diaphragm, cervical cap, or spermicide increased risk almost twofold (OR = 1.76, 95 percent CI: 1.25, 2.48). Length of partnership and new sex partner since enrollment were not significantly associated with risk of a second UTI. When both variables were included in the model, having a new sex partner was positively, but not statistically, significantly associated with risk of second UTI (OR = 1.76, 95 percent CI: 0.47, 6.59), and a partner of less than 4 months duration had no association (OR = 1.04, 95 percent CI: 0.30, 3.61) (data not shown). Thus, we included only the length of the relationship in the base model. The remaining potential risk factors were added to the base model one at a time. Adjustment for behavioral variables brought the effects

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TABLE 3. Continued

Variable	Coefficient	SE	*p* value	OR	95% CI
Wait to urinate sometimes/frequently/always (vs. never)	−0.1957	0.3232	0.54	0.82	0.44, 1.55
Wiping after urination (vs. front to back)					
Wipe back to front	−0.0659	0.3859	0.86	0.94	0.44, 1.99
Wipe either direction/other pattern	0.2973	0.3793	0.43	1.35	0.64, 2.83
Urination around sex (vs. before and after sex)					
Urinate only before sex	−0.5054	0.7464	0.50	0.60	0.14, 2.61
Urinate only after sex	−0.5059	0.5515	0.36	0.60	0.20, 1.78
Urinate neither before nor after sex	0.2235	0.6609	0.74	1.25	0.34, 4.57
Cigarettes	0.0639	0.3653	0.86	1.07	0.52, 2.18
Antibiotics during previous 2 weeks	0.6158	0.3785	0.10	1.85	0.88, 3.89
First UTI treatment regimen (vs. trimethoprim-sulfa)					
Nitrofurantoin	−0.0916	0.3415	0.79	0.91	0.47, 1.78
Other	−0.7563	0.6504	0.25	0.47	0.13, 1.68
Aerobactin (*aer*)	0.1706	0.6667	0.80	1.19	0.32, 4.38
Capsule (*KpsMT*)	0.2273	0.6454	0.72	1.26	0.35, 4.45
Cytotoxic necrotizing factor I (*cnf1*)	0.0524	0.6944	0.94	1.05	0.27, 4.11
Dr binding adhesins (*drb*)	0.4352	0.7217	0.55	1.55	0.38, 6.36
Hemolysin (*hly*)	−0.1406	0.6839	0.84	0.87	0.23, 3.32
Outer membrane protein T (*ompT*)	0.1841	0.6460	0.78	1.20	0.34, 4.26
P pili (*prf*)	0.0186	0.6632	0.98	1.02	0.28, 3.74
S fimbril adhesin (*sfa*)	0.0681	0.6917	0.92	1.07	0.28, 4.15

* All parameter estimates adjusted for the frequency of vaginal intercourse, condom use, use of spermicides, no birth control method, length of current sexual relationship, and time. Behaviors were assessed at 2, 4, and 6 months after first UTI and at time of recurrence. Fifty-three second UTI were detected after initial *E. coli* UTI. Bacterial virulence factors are relative to bacteria having type I pili (*fim*) only (see Materials and Methods).

† SE, standard error; OR, odds ratio; CI, confidence interval.

‡ Mutually exclusive categories.

of bacterial virulence factors closer to the null. For the remaining variables, the confidence intervals are wide, and the estimated odds ratios differ only slightly from rate ratios presented in the bivariate analyses.

DISCUSSION

The identification of risk factors for recurrent UTI has been complicated by the multiagent nature of the syndrome and the interactions of bacterial virulence factors, host behaviors, and host characteristics. Comparisons of the bacterial virulence characteristics of *E. coli* causing recurrent UTI with those causing first UTI have been relatively uninformative (19), and comparison of behaviors of women with recurrent UTI with those with first UTI often highlights factors that change in response to UTI rather than risk factors for recurrent UTI (20). Host characteristics, including secretor status (21) and vaginal flora (22), have been associated with recurrent UTI, but their relative importance remains to be shown. We focused upon risk factors for second UTI, subclassifying first UTI into those caused by *E. coli* and by non-*E. coli*, and used molecular techniques to further subclassify second UTI into second UTI due to the same or a different uropathogen.

We observed a higher rate of second UTI when the first UTI was caused by *E. coli* than when it was caused by non-*E. coli* (24 vs. 8 percent). Women with first UTI due to *E. coli* were more likely than were those with non-*E. coli* first UTI to have engaged in vaginal intercourse prior to their first UTI. We found no difference in other behaviors, including urination habits around intercourse, but our numbers are small, limiting our ability to detect associations. We are unaware of any previous reports of different recurrence rates for non-*E. coli* UTI or of the stronger association of *E. coli* first UTI with vaginal intercourse.

Among women with first UTI caused by *E. coli*, vaginal intercourse also increased rate of second UTI, regardless of whether the second UTI was caused by the same or a different uropathogen. Vaginal intercourse has been associated with first and recurrent UTI in the same (8, 9, 20) and similar (4) populations. When a uropathogen is already present in the vagina or periurethral area, the movement of uropathogens and trauma associated with vaginal intercourse may increase risk of symptomatic infection. Vaginal intercourse may also introduce a uropathogen from a sex partner or an internal reservoir.

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The significantly protective effect of drinking carbonated beverages on risk of second UTI is hard to explain. When the Michigan first UTI cases were compared with population controls (8), drinking carbonated beverages was an apparent risk factor for acquiring first UTI. These results require further study for proper interpretation.

One third of second UTI after *E. coli* UTI were caused by the same *E. coli*, and the timing of second UTI was different than that for second UTI caused by a different pathogen. Recurrence with the same *E. coli* was concentrated in the first 3 months after first UTI, while recurrence with a different uropathogen was spread more evenly throughout the follow-up period. These results are consistent with those of a Finnish study that followed 179 nonpregnant women with community-acquired *E. coli* cystitis (5). That study also found that one third of the recurrences were with the index strain and that recurrences with the index strain occurred more frequently in the first few months after the index UTI. An internal reservoir may serve as source of reinfection; this reservoir may be lost or replaced by a new uropathogen over time. We did not collect vaginal or fecal specimens and so cannot comment on whether second infection was from an internal reservoir or a new infection. While type or duration of treatment may be important in removing an internal reservoir, we did not find an association between type or duration of therapy for first UTI and risk of second UTI either with the same or a different uropathogen.

Of the nine different *E. coli* virulence factors studied here, only Dr was positively associated with the risk of a second UTI and that only weakly and not significantly. This is consistent with the results of the Finnish study, which examined expression of virulence factors (MR adhesin, P fimbriae, non-P MR adhesins, type IC fimbriae, hemolysin, and serotypes K5, K, O2, O8, and O75) and found that they did not increase the risk of recurrence during a 1-year follow-up period (5). However, they found that strains with these factors were more likely to persist and cause a second infection. We found a negative association between the presence of P pili, S fimbrial adhesin, cytotoxic necrotizing factor I, and hemolysin and recurrence with the same strain and no association of these factors with a second UTI due to a different uropathogen.

In conclusion, we followed women with a first UTI in order to avoid the methodological pitfalls associated with studying women with a history of varying numbers of previous UTI. This strategy allowed us to confirm the role of several behavioral risk factors and to identify the importance of the genus of the initial uropathogen on risk of second UTI. Although risk of second UTI is strongly influenced by sexual behavior, *E. coli* first UTI are more likely than are non-*E. coli* first UTI to result in a second UTI within 6 months.

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