A PROSPECTIVE STUDY OF ASYMPTOMATIC BACTERIURIA IN SEXUALLY ACTIVE YOUNG WOMEN

THOMAS M. HOOTON, M.D., DELIA SCHOLES, PH.D., ANN E. STAPLETON, M.D., PACITA L. ROBERTS, M.S., CAROL WINTER, A.R.N.P., KALPANA GUPTA, M.D., M.P.H., MANSOUR SAMADPOUR, PH.D., AND WALTER E. STAMM, M.D.

ABSTRACT

Background Asymptomatic bacteriuria is common in young women, but little is known about its pathogenesis, natural history, risk factors, and temporal association with symptomatic urinary tract infection.

Methods We prospectively evaluated 796 sexually active, nonpregnant women from 18 through 40 years of age over a period of six months for the occurrence of asymptomatic bacteriuria (defined as at least 10^5 colony-forming units of urinary tract pathogens per milliliter). The women were patients at either a university student health center or a health maintenance organization (HMO). Periodic urine cultures were taken, daily diaries were kept, and regularly scheduled interviews were performed. *Escherichia coli* strains were tested for hemolysin, the *papG* genotype, and the ribosomal RNA type.

Results The prevalence of asymptomatic bacteriuria (the proportion of urine cultures with bacteriuria in asymptomatic women) was 5 percent (95 percent confidence interval, 4 percent to 6 percent) among women in the university group and 6 percent (95 percent confidence interval, 5 percent to 8 percent) among women in the HMO group. Persistent asymptomatic bacteriuria with the same *E. coli* strain was rare. Symptomatic urinary tract infection developed within one week after 8 percent of occasions on which a culture showed asymptomatic bacteriuria, as compared with 1 percent of occasions when asymptomatic bacteriuria was not found ($P<0.001$). Asymptomatic bacteriuria was associated with the same risk factors as for symptomatic urinary tract infection, particularly the use of a diaphragm plus spermicide and sexual intercourse.

Conclusions Asymptomatic bacteriuria in young women is common but rarely persists. It is a strong predictor of subsequent symptomatic urinary tract infection. (N Engl J Med 2000;343:992-7.)

QUANTITATIVE analysis of bacteria in urine cultures was developed several decades ago[1-4] to establish reliable criteria for discriminating between infection and contamination in asymptomatic subjects, with the expectation that asymptomatic infection might be associated with pyelonephritis, hypertension, renal disease, and complications of pregnancy.[5-8] In studies of asymptomatic bacteriuria, counts of at least 10^5 colony-forming units per milliliter usually predicted persistently high levels of bacteriuria, whereas counts of less than 10^5 colony-forming units per milliliter usually meant persistently low levels of bacteriuria, with distinctive microflora for each group.[2,4,5] Moreover, high concentrations of pathogenic bacteria in serial voided urine specimens had the same predictive value as the presence of bacteria in single catheter specimens.[4,5] Therefore, the presence of at least 10^5 colony-forming units of the same urinary tract pathogen per milliliter in consecutive voided urine specimens has been widely adopted as the criterion identifying potentially important bacteriuria in asymptomatic women.[7,8] According to this definition, the prevalence of asymptomatic bacteriuria in healthy women 18 to 40 years of age is approximately 5 percent, and it increases with age to 20 percent or more in ambulatory elderly women.[8-11]

Even though asymptomatic bacteriuria is common and appears to be associated with adverse outcomes in some groups, such as pyelonephritis in pregnant women,[4,7,8,12] little is known about its pathogenesis, natural history, risk factors, and temporal association with symptomatic urinary tract infection. We undertook this study to evaluate these factors in healthy women, using a prospective study design and molecular typing methods.

METHODS

Study Design

The overall study design and methods have been described previously.[13] Briefly, the study was conducted from 1989 to 1994 at the University of Washington Student Health Center and at a health maintenance organization (HMO), the Group Health Cooperative of Puget Sound, both in Seattle. The study was approved by the review committees of both institutions, and all the women gave written informed consent. Women were eligible for inclusion if they were healthy, were between 18 and 40 years old, were about to start using a new method of contraception (oral contraceptive, diaphragm plus spermicide, spermicide alone, or cervical cap) or had started using a new method within 6 weeks before enrollment, and had had no more than one urinary tract infection in the previous 12 months. Women were ineligible if they were pregnant or planning to become pregnant, had a chronic illness requiring medical supervision, had taken an antimicrobial drug within the previous 14 days, or had a known anatomical or functional abnormality of the urinary tract.

From the Departments of Medicine (T.M.H., A.E.S., P.L.R., C.W., K.G., W.E.S.), Epidemiology (D.S.), and Environmental Health (M.S.), University of Washington School of Medicine and School of Public Health and Community Medicine; and the Center for Health Studies, Group Health Cooperative of Puget Sound (D.S.) — all in Seattle. Address reprint requests to Dr. Hooton at Harborview Medical Center, 325 Ninth Ave. (Box 359930), Seattle, WA 98104, or at hooton@u.washington.edu.

Evaluation of Study Subjects

At the initial visit, the women were interviewed with the use of a standardized questionnaire. A midstream urine specimen was obtained for evaluation of pyuria (at the university site only) and bacteriuria, and blood and saliva were obtained for determination of ABO-blood-group secretor status. The women were then instructed to record in a diary the days on which the following occurred: sexual intercourse, use of contraception (and type used), vaginal and urinary symptoms, and antibiotic use. At each subsequent visit to the clinic, the women underwent a directed history taking, their diaries were reviewed to ensure compliance, and a midstream urine specimen was collected. The women in the university group were asked to return to the clinic weekly for four weeks and then monthly, for a total of six months. The women in the HMO group were asked to return every two months for six months. In the alternate months, these women were asked to bring or mail to the clinic an agar-coated slide (Oxoid, Unipath, Ogdensburg, N.Y.) that had been dipped in urine, which was then cultured to identify and quantify urinary bacteria.

Laboratory Studies

Midstream urine specimens were collected for aerobic bacterial cultures and evaluated microbiologically by previously described methods.[14] Pyuria was defined as the presence of at least 8 leukocytes per cubic millimeter of urine, as determined by a hemacytometer. ABO-blood-group secretor status and *Escherichia coli* hemolysin production and *papG* genotypes (at the university site only) were determined in blinded fashion by previously described methods.[15-17] The *papG* gene encodes the tip adhesin on P fimbriae.

Genomic-DNA isolation, restriction-endonuclease digestion, gel electrophoresis, and Southern blot hybridization were performed as previously described.[18] Total *E. coli* ribosomal RNA (Sigma, St. Louis) was radioactively labeled by extension of random primers with the use of reverse transcriptase.[19] Ribotyping was performed with the use of *Pvu*II and *Eco*RI. Only isolates with 100 percent matching in the restriction-fragment–length polymorphism patterns were classified as identical.

Definition of Asymptomatic Bacteriuria and Symptomatic Urinary Tract Infection

Asymptomatic bacteriuria was defined by the presence of at least 10^5 colony-forming units of a urinary tract pathogen per milliliter in a culture of a midstream urine specimen obtained from an asymptomatic woman on a routine scheduled visit. An episode of asymptomatic bacteriuria was defined by the presence of either one isolated culture with evidence of asymptomatic bacteriuria or two or more consecutive cultures with evidence of asymptomatic bacteriuria due to the same species and, if *E. coli* was present, the same ribotype, with no intervening antibiotic therapy. A woman was considered to have a symptomatic urinary tract infection if she had dysuria, urinary frequency, or urinary urgency together with at least 10^2 urinary tract pathogens per milliliter. In the absence of a urine culture, a woman was considered to have a symptomatic urinary tract infection if she had received a diagnosis of a urinary tract infection from a health care provider or had been treated for urinary symptoms with an antimicrobial drug.[13] Organisms considered to be urinary tract pathogens included gram-negative bacilli, *Staphylococcus saprophyticus, S. aureus,* enterococci, and group B streptococci. Coagulase-negative staphylococci, alpha-hemolytic streptococci, lactobacilli, diphtheroids, and mixed gram-positive flora were categorized as nonpathogens.

Statistical Analysis

The prevalence of asymptomatic bacteriuria was determined by dividing the total number of cultures with evidence of asymptomatic bacteriuria by the total number of routine scheduled urine cultures performed. Cultures performed when the woman was taking an antimicrobial drug for urinary tract infection were excluded from these analyses. For the analysis of the incidence of asymptomatic bacteriuria, women were considered to be at risk when they had neither asymptomatic bacteriuria nor symptomatic urinary tract infection. The incidence was determined by dividing the total number of episodes of asymptomatic bacteriuria by the total number of person-years at risk.

Univariate analyses to identify risk factors for asymptomatic bacteriuria were performed with age, marital status, race, history of urinary tract infections, ABO-blood-group secretor status, contraceptive use, and frequency of sexual intercourse as variables. Contraceptive use and frequency of intercourse were based on data reported in the diary, except that oral-contraceptive use was assumed to be daily as prescribed. We adjusted for multiple observations per woman by fitting logistic regressions with generalized estimating equations.[20] This procedure enabled us to compute adjusted prevalences and their 95 percent confidence intervals, as well as to evaluate several risk factors simultaneously in multivariate models. All statistical tests were two-sided.

RESULTS

Three-hundred forty-eight women in the university group and 448 women in the HMO group were enrolled in the study and had at least one follow-up visit. There were 146 person-years of follow-up in the university group and 177 person-years in the HMO group. As compared with those in the university group, the women in the HMO group were older (mean age, 29 vs. 23 years), more likely to be married (61 percent vs. 10 percent), and more likely to be white (88 percent vs. 79 percent).[13] During the study, there were 98 symptomatic urinary tract infections (0 to 3 per woman) in the university group and 82 (0 to 7 per woman) in the HMO group.[13]

Colony Counts, Pyuria, and *E. coli* Virulence Characteristics

A total of 3040 urine cultures (2 to 10 per woman) were obtained from asymptomatic women in the university group and 2691 (1 to 8 per woman) from women in the HMO group. The distribution of counts of colony-forming units of pathogenic organisms and the percentage of cultures with evidence of pyuria according to colony count are shown in Table 1. In both groups combined, there were 4530 cultures for which one or more follow-up cultures were available. On 68 (42 percent) of the 160 occasions when a culture from an asymptomatic woman had at least 10^5 colony-forming units of *E. coli* per milliliter, but on only 113 (3 percent) of the 4370 occasions when the culture had fewer than 10^5 colony-forming units of *E. coli* per milliliter, the next scheduled culture had at least 10^5 colony-forming units of *E. coli* per milliliter ($P<0.001$). Pyuria was associated with higher colony counts (Table 1). Moreover, pyuria was present in 9 (16 percent) of 58 episodes of asymptomatic bacteriuria defined by one isolated culture, 6 (32 percent) of 19 episodes of asymptomatic bacteriuria defined by two or more consecutive cultures, and 81 (94 percent) of 86 symptomatic urinary tract infections.

There were no differences between asymptomatic and symptomatic women in the proportion of *E. coli*

TABLE 1. COLONY COUNTS OF URINARY TRACT PATHOGENS AND FREQUENCY OF PYURIA IN URINE SAMPLES COLLECTED FROM ASYMPTOMATIC WOMEN DURING ROUTINE STUDY VISITS.

NO. OF COLONY-FORMING UNITS/ml	UNIVERSITY HEALTH CENTER (N=3040)		HMO (N=2691)
	CULTURES*	FRACTION WITH PYURIA†	CULTURES*
	no. (%)	no./total no. (%)	no. (%)
$<10^1$	1884 (62)	55/1874 (3)	1499 (56)
$\geq 10^1$ to $<10^3$	579 (19)	18/575 (3)	492 (18)
$\geq 10^3$ to $<10^4$	274 (9)	14/271 (5)	319 (12)
$\geq 10^4$ to $<10^5$	160 (5)	16/156 (10)	229 (9)
$\geq 10^5$	143 (5)	34/143 (24)	152 (6)

*Because of rounding, not all percentages add to 100.

†Pyuria was assessed only in the university group; in 21 cultures there was no assessment of pyuria.

strains that were positive for hemolysin and *papG*. Thus, hemolysin was produced by 293 (30 percent) of the 976 *E. coli* strains that were present in quantities of less than 10^5 colony-forming units per milliliter in asymptomatic women, 76 (33 percent) of the 232 *E. coli* strains that caused asymptomatic bacteriuria, and among women in the university group, 26 (34 percent) of the 76 *E. coli* strains that caused symptomatic urinary tract infections. Likewise, among women in the university group, there were no differences among 122 *E. coli* strains that caused asymptomatic bacteriuria and 78 *E. coli* strains that caused symptomatic urinary tract infections in the proportions with the P adhesin gene *papG* (39 percent and 41 percent, respectively) or with the class I, II, or III *papG* alleles.

Asymptomatic Bacteriuria

Prevalence and Incidence

The prevalence of asymptomatic bacteriuria, adjusted for multiple observations per woman, was 5 percent (95 percent confidence interval, 4 percent to 6 percent) in the university group and 6 percent (95 percent confidence interval, 5 percent to 8 percent) in the HMO group. *E. coli* was the urinary tract pathogen in 110 (77 percent) of the 143 cultures with asymptomatic bacteriuria among women in the university group and 122 (80 percent) of the 152 cultures with asymptomatic bacteriuria among women in the HMO group. Eighty-three women in the university group (24 percent) and 96 women in the HMO group (21 percent) had at least one episode of asymptomatic bacteriuria. Episodes of asymptomatic bacteriuria defined by at least two consecutive cultures with bacteriuria occurred in 19 women in the university group (5 percent) and 21 women in the HMO group (5 percent). Episodes of asymptomatic bacteriuria lasting at least two months occurred in only three women in the university group and two women in the HMO group. Only one woman had asymptomatic bacteriuria with the same *E. coli* ribotype at all study visits.

The incidence of asymptomatic bacteriuria was 0.39 episode per person-year among women in the university group and 0.53 episode per person-year among women in the HMO group.

Molecular Characterization of E. coli *Strains Causing Asymptomatic Bacteriuria*

We evaluated 65 episodes of asymptomatic *E. coli* bacteriuria in women in the university group. Restriction-fragment–length polymorphism typing (ribotyping) was performed on all but one *E. coli* strain isolated from a follow-up culture. The results after the initial cultures from these 65 episodes are shown in Figure 1. In 34 cases (52 percent), the next evaluation revealed neither asymptomatic bacteriuria nor symptomatic urinary tract infection; in 21 (32 percent), the next evaluation revealed asymptomatic bacteriuria (17 [26 percent] involving the woman's original strain of *E. coli*); and in 10 (15 percent), the next evaluation revealed a symptomatic urinary tract infection, 5 of which were caused by the woman's original strain of *E. coli*.

Eight urinary tract infections and six episodes of asymptomatic bacteriuria occurred in women whose previous episodes of asymptomatic bacteriuria had ended earlier. These more distant episodes were less likely to be caused by *E. coli* strains identical to the women's original *E. coli* strains than in the cases of consecutively isolated strains described above.

Risk of Symptomatic Urinary Tract Infection

In both groups combined, 23 (8 percent) of 295 cultures with asymptomatic bacteriuria were followed by a symptomatic urinary tract infection within one week (each of the 15 strain pairs for which information was available were of the same species and, for *E. coli*, the same ribotype), as compared with 44 (1 percent) of 5436 cultures with less than 10^5 colony-forming units of urinary pathogens ($P<0.001$ for both study sites). Of the 34 cultures with asymptomatic bacteriuria and pyuria, 5 (15 percent) were followed within one week by a symptomatic urinary tract infection. Asymptomatic bacteriuria was also associated with an increased risk of urinary tract infection within one month.

Risk Factors for Asymptomatic Bacteriuria

In univariate analyses, factors significantly associated with asymptomatic bacteriuria were the use of a diaphragm plus spermicide, sexual intercourse, the use of spermicide alone, and the use of a cervical cap. There were no significant associations between asymp-

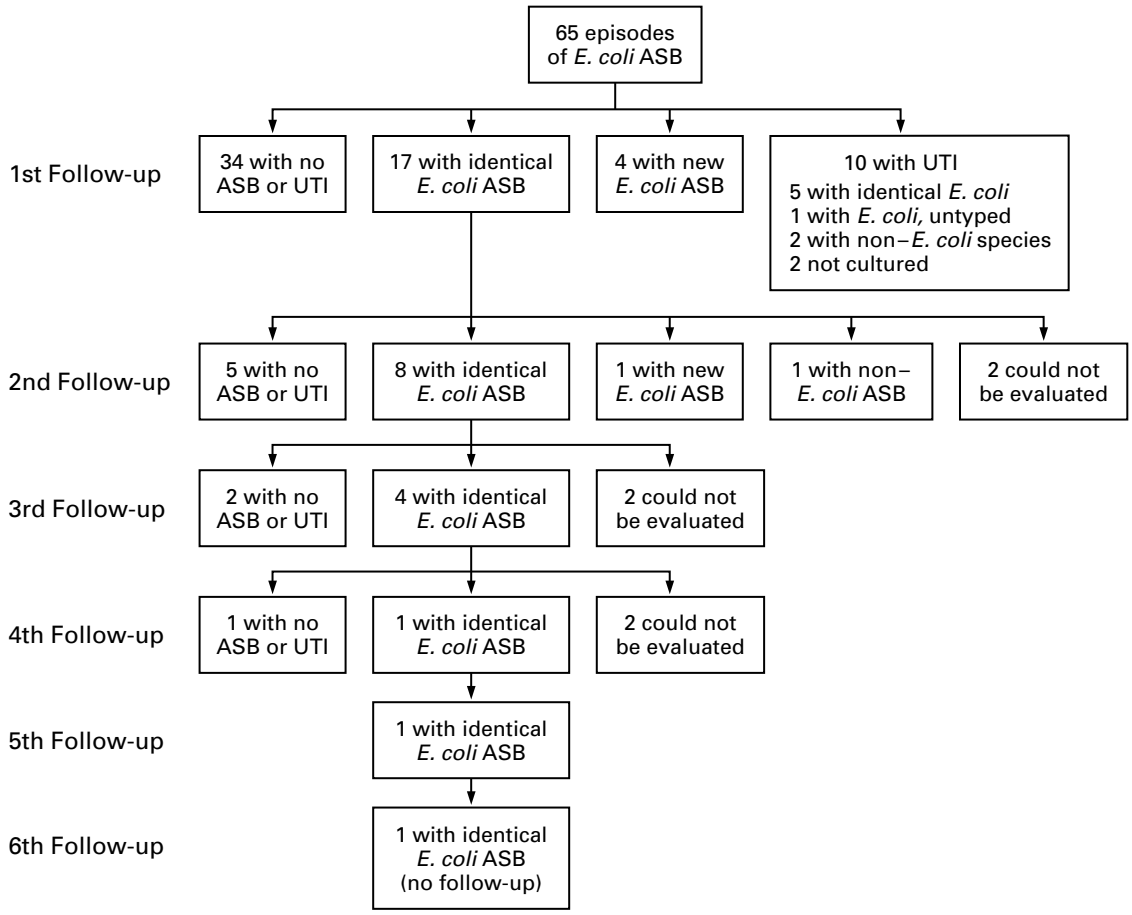

Figure 1. Results after the First Culture Indicating Asymptomatic *E. coli* Bacteriuria in 65 Episodes.

Asymptomatic bacteriuria (ASB) was considered to be present when at least 10^5 colony-forming units of urinary tract pathogens per milliliter were found. "Identical *E. coli*" denotes a strain with the same pattern of restriction-fragment–length polymorphisms as the *E. coli* strain in the prior culture. "New *E. coli*" denotes a strain with a different pattern. Episodes that could not be evaluated at a subsequent follow-up visit involved women who finished the study, received antibiotic therapy, or were lost to follow-up. UTI denotes symptomatic urinary tract infection.

tomatic bacteriuria and age, marital status, race, history with respect to symptomatic urinary tract infection, or secretor status. In multivariate analyses, the recent use of a diaphragm plus spermicide and recent sexual intercourse remained strongly associated with asymptomatic bacteriuria in both groups, whereas use of spermicide alone and use of a cervical cap were significantly associated in only one of the groups (Table 2).

DISCUSSION

The adjusted prevalence of asymptomatic bacteriuria was 5 percent among women in the university group and 6 percent among women in the HMO group. Twenty-four percent of women in the university group and 21 percent of women in the HMO group had at least one episode of asymptomatic bacteriuria. Episodes of asymptomatic bacteriuria consisting of at least two consecutive cultures with asymptomatic bacteriuria occurred in 5 percent of the women in both groups. These rates of asymptomatic bacteriuria are similar to those described in nonpregnant[8-10] and pregnant[5,8] women, but higher than those reported in healthy schoolgirls.[21] Episodes of asymptomatic bacteriuria lasting at least two months, on the other hand, were very uncommon, occurring in fewer than 1 percent of women in both groups, and only one woman had asymptomatic bacteriuria at all study visits. On the basis of monthly cultures from asymptomatic women, the incidence of asymptomatic bacteriuria was 0.39 episode per person-year among women in the university group and 0.53 episode per person-year among women in the HMO group. These are minimal estimates, since some episodes of asymptomatic bacteriuria are likely to have occurred between the monthly scheduled cultures.

TABLE 2. RISK FACTORS FOR ASYMPTOMATIC BACTERIURIA ACCORDING TO STUDY SITE.*

RISK FACTOR	UNIVERSITY HEALTH CENTER (N=323)		HMO (N=418)	
	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Recent use of diaphragm plus spermicide	1.6 (1.4–1.9)	<0.001	1.5 (1.2–1.8)	<0.001
Recent use of cervical cap	1.4 (1.1–1.7)	0.005	1.1 (0.8–1.4)	0.62
Recent use of spermicide alone	1.4 (0.6–3.2)	0.40	2.4 (1.4–4.4)	0.003
Recent sexual intercourse	1.3 (1.1–1.4)	<0.001	1.2 (1.1–1.5)	0.007
History of ≥2 urinary tract infections in lifetime	0.6 (0.3–1.3)	0.20	1.9 (1.1–3.4)	0.02

*Values have been adjusted for age and marital status. Use of a diaphragm plus spermicide, use of a cervical cap, and sexual intercourse were fitted as continuous variables according to the number of days of exposure (as recorded in the study diary) in the seven days before the urine sample was obtained. The relative risks indicate the risk associated with one day of exposure as compared with none. Use of spermicide alone was fitted as a dichotomous variable (any exposure vs. no exposure in the previous seven days). Only clinic visits with complete data for all the risk factors of interest were included. Twenty-five asymptomatic women in the university group and 30 in the HMO group had no clinic visits for which complete data were available on these risk factors. CI denotes confidence interval.

The use of the clean-void midstream method of collection and quantitative urine cultures to differentiate infection from contamination and to delineate the natural history of bacteriuria is well established.[3-5] In these studies, there was an 80 percent likelihood that a voided midstream urine specimen with at least 10^5 gram-negative bacteria per milliliter would be followed by a specimen with a similarly high colony count, and two consecutive voided specimens were therefore needed to provide the same degree of accuracy as a single urine specimen obtained through a catheter in predicting bladder bacteriuria.[4,5]

In our study, only 26 percent of 65 cultures showing asymptomatic *E. coli* bacteriuria were followed by cultures showing asymptomatic bacteriuria with the same strain of *E. coli*, and persistent asymptomatic bacteriuria was rare. These numbers are considerably lower than those reported previously[4,5] and suggest that the majority of episodes of asymptomatic *E. coli* bacteriuria are transient. The quality of our method of midstream urine collection is supported by the finding that only 10 to 14 percent of voided urine cultures had 10^4 or more colony-forming units per milliliter, which is similar to the 7 to 27 percent reported by Kass.[4]

Our finding that asymptomatic bacteriuria is associated with an increased risk of symptomatic urinary tract infection is in agreement with findings of other investigators.[5,6,22,23] This association was stronger if pyuria was present, suggesting that some episodes of asymptomatic bacteriuria may be early or subclinical urinary tract infections that eventually lead to the development of symptoms. Further evidence supporting this hypothesis comes from the observation that paired *E. coli* strains from episodes of asymptomatic bacteriuria and subsequent symptomatic urinary tract infection in a given woman were usually identical if the urine cultures were consecutive, but were usually different if there were one or more intervening negative urine cultures.

There are few other studies with which to compare our data on risk factors. In a case–control study, asymptomatic bacteriuria was associated with diaphragm use but not with sexual intercourse.[24] In the two groups of women we studied prospectively, asymptomatic bacteriuria was associated with the same factors that predispose women to symptomatic urinary tract infection,[13] particularly the use of a diaphragm plus spermicide and sexual intercourse.

Several virulence factors have been associated with *E. coli* strains that cause symptomatic urinary tract infections, especially pyelonephritis, but virulence factors have been less clearly defined for strains that cause asymptomatic bacteriuria.[25,26] Hemolysin and *papG*, the gene that encodes the tip adhesin on P fimbriae, were tested in this study because these two factors have both been found to be more prevalent among strains that cause clinically severe urinary tract infections.[26] In our study, the proportions of *E. coli* strains that were positive for hemolysin and *papG* were almost identical among women with asymptomatic bacteriuria and those with symptomatic urinary tract infection. In addition, the data on ribosomal RNA typing show that identical *E. coli* strains can cause either asymptomatic bacteriuria or symptomatic urinary tract infection in the same woman. The similarity of risk factors for both asymptomatic bacteriuria and symptomatic urinary tract infection further suggests that *E. coli* strains that cause asymptomatic bacteriuria and symptomatic urinary tract infection in adult women come from the same pool of fecal strains.

The generalizability of our findings is strengthened by the prospective study design, the daily recording of information of interest, the laboratory

characterization of the *E. coli* strains, and the similarity of the findings in two different groups of women, one of which was representative of the women in the Puget Sound region.[13] Our findings are consistent with the hypothesis that asymptomatic bacteriuria is a frequent occurrence that results when urinary tract pathogens, particularly *E. coli*, enter the bladder without causing symptoms. The pathogens are usually eliminated by host defense factors, but they may persist for a short or, rarely, a long time or result in a symptomatic urinary tract infection. Over time, the process may be repeated with a different strain. It remains to be determined why symptomatic urinary tract infection occurs in only a small proportion of women with high levels of bacteriuria.

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