

Recurrence of Urinary Tract Infection in a Primary Care Setting: Analysis of a 1-Year Follow-up of 179 Women

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In a prospective study, 179 adult women (age range, 17–82 years) were followed up for 12 months after an index episode of community-acquired cystitis caused by *Escherichia coli*. Episodes of symptomatic urinary tract infection (UTI) were recorded, and urinary isolates were compared with the index episode isolate; 147 UTI episodes were detected during the follow-up. Of these episodes, 131 were classified as recurrences occurring at least 1 month after the index episode; 44% of the patients had recurrences. A history of UTI increased the risk of recurrence; only 11.8% of the 17 patients without previous episodes of UTI had at least one recurrence, while 47.5% of those with previous episodes had at least one recurrence (OR, 6.8; univariate logistic regression). *E. coli* caused 78% of the recurrent episodes. Phenotypic and genotypic analysis of *E. coli* strains showed that one-third of the recurrences were caused by the index episode strain, which could persist and cause recurrences throughout the 1-year follow-up period. The prevalence of adhesins or other identified virulence factors for UTI among the recurrence strains was identical to that among the index episode strains. The presence of these factors did not affect the risk of recurrence but did increase the likelihood that the index episode strain would persist and cause recurrent episodes of UTI.

Urinary tract infection (UTI) is a common cause of morbidity in otherwise healthy women. A characteristic feature of UTI is its tendency to recur. Most recurrences are not due to inadequate treatment of the original infection but are thought to be reinfections, each caused by introduction of a new microorganism from the fecal/perineal flora into the urinary tract [1–3]. However, the original strain may remain as a part of the intestinal flora and may even cause a reinfection of the urinary tract months after the index episode [3–5].

The events that may lead to an episode of UTI begin when the intestine becomes colonized with a bacterial strain possessing the necessary combination of virulence factors that enable it to ascend the urethral mucosa and subsequently colonize and infect the urinary tract [5]. The essential role of P fimbriae in the pathogenesis of acute pyelonephritis in immunocompetent children and adults has been confirmed by several groups of investigators [6–19]. Hemolysin and aerobactin are also regarded as virulence-enhancing determinants, at least in upper UTI. Non-P mannose-resistant (MR) (e.g., DR-blood-group-specific) adhesins apparently play a pathogenetic role in cystitis [20–25].

The pathogenesis of recurrent UTI is less well defined, and the role of microbial characteristics in it has not been studied.

Two main hypotheses have been put forward to explain the increased risk of some women for recurrent UTIs [26, 27]. The first hypothesis, which was introduced by Stamey and colleagues, suggests that the local defense mechanisms of these women are defective and render them more susceptible to periurethral colonization [28, 29]. The second hypothesis suggests that the first episode causes changes in host resistance [30]. In either case, it could be surmised that the role of microbial virulence factors might be less in recurrent UTI than in the first episode.

To evaluate the role of bacterial virulence factors in the recurrence of lower UTI, we prospectively followed up 179 adult women who had had acute community-acquired cystitis caused by *Escherichia coli* and registered all their UTI episodes during 12 months after the index episode. Bacterial strains isolated from the urine at the time of each UTI episode were identified, and *E. coli* strains were typed according to somatic (O) and capsular (K) antigens, expression of fimbriae and other adhesins, hemolysin production, and ribotype. These analyses permitted an accurate assessment of the role of the original infecting strain vs. the new infecting strain and showed that the original strain was in fact responsible for one-third of reinfections occurring 1–12 months after the index episode.

Patients

A total of 179 consecutive nonpregnant women with community-acquired cystitis caused by *E. coli* were followed up for 12 months after an index episode of cystitis (178 of these patients have been previously described [23]). The index episode was treated for 5–7 days by conventional drugs (55%, trimethoprim; 23%, nitrofurantoin; 10%, pivmecillinam; 10%,

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co-trimoxazole; and 2%, some other drug). The mean duration of treatment was 6.1 days (range, 3–10 days; average, 5.5 days [for trimethoprim or co-trimoxazole] and 7 days [for pivmecillinam or nitrofurantoin]). All UTI episodes during the follow-up were registered. The mean age of the patients was 48 years (range, 17–82 years; median, 51 years). During the follow-up period, each patient was under the care of one of three physicians (R. I., P. K., and P. L.) and one of two nurses participating in this study. In addition to the scheduled control visits, the patients were encouraged to consult the community health center only when UTI symptoms occurred (see below). Clinical examination, laboratory studies of blood for infection parameters (C-reactive protein [CRP] level, erythrocyte sedimentation rate, and WBC count), urinary sedimentation, and urine culture were performed at the following times: the beginning of the study (registration of the index episode), 2 weeks after the index episode, when the patient had clinical symptoms of recurrent UTI, 2 weeks after a symptomatic episode of UTI, and the end of the follow-up period (12 months after the index episode).

Before entering this study, 17 women (9.5%) had not had any previous episodes of UTI, while the remaining patients had had sporadic or recurrent episodes [23]. Eighteen patients had conditions weakly predisposing to UTI: eight had diabetes, and 10 had minor anatomic abnormalities. Otherwise, there were no medical illnesses predisposing to UTI.

An episode of UTI during the follow-up period was defined as significant bacteriuria (at least 10^4 cfu for symptomatic patients and at least 10^5 cfu for asymptomatic patients). Recurrence of UTI was defined as an episode occurring at least 1 month after the index episode. Acute cystitis was defined as dysuria, frequency and urgency of urination in the absence of flank pain, fever (temperature, $<38^\circ\text{C}$), and significant bacteriuria. The diagnosis of acute pyelonephritis was based on clinical symptoms and signs (CRP level, ≥ 30 mg/L; pyuria; temperature, $\geq 38^\circ\text{C}$; and significant bacteriuria).

Methods

Bacteria

E. coli and other gram-negative and gram-positive bacteria were identified by standard methods [31]. The *E. coli* strains were stored and subcultured for further analyses as previously described [32].

Phenotyping of *E. coli* Strains

MR hemagglutinins were detected by agglutination of erythrocytes from humans of blood group O as previously described [6]. P fimbriation was detected by P-(Gal-Gal)-specific agglutination (PF Test; Orion Diagnostica, Espoo, Finland) as previously described [33]. Strains showing MR hemagglutination

without expression of P fimbriae were defined as having non-P MR adhesins [32].

The identification of type 1C fimbriae was based on bacterial agglutination with specific polyclonal and monoclonal antibodies, which were kindly provided by Dr. A. Pere (Orion Diagnostica). Strains showing any agglutination were further analyzed by indirect immunofluorescence with monoclonal antibody to type 1C fimbriae [34, 35].

The production of hemolysin was tested on sheep blood agar plates. Strains producing a clear halo in culture after overnight incubation at 35°C were defined as hemolysin-positive. O:K serotyping of the strains was performed as previously described [32]. Susceptibility testing of the epidemiologically interesting strains was performed by a commercial disk diffusion method (Neo-Sensitabs; Rosco Diagnostica, Taastrup, Denmark) with the following antibiotics: ampicillin, cephalixin, cephalothin, cefuroxime, cefotaxime, chloramphenicol, cinoxacin, ciprofloxacin, gentamicin, nalidixic acid, nitrofurantoin, mecillinam, polymyxin B, sulfonamide, tetracycline, and trimethoprim.

Genotyping of *E. coli* Strains

Restriction fragment length polymorphism of the rRNA genes from isolates from patients with recurrences that differed phenotypically only slightly or were nontypeable by serotyping was determined [36, 37]. Chromosomal DNA from the strains was isolated with a DNA extractor (Applied Biosystems, Foster City, California) and was digested with *Hind*III (Boehringer Mannheim, Mannheim, Germany) according to the manufacturer's instructions. After Southern blotting onto a Hybond — N+ nylon membrane (Amersham International, Amersham, United Kingdom), the plasmid pKK3535 carrying the 5S, 16S, and 23S rRNA genes [38] was used as a probe. A commercial kit (DIG; Boehringer Mannheim) was used for labeling the probe, hybridization, and detection of the hybrids [37]. If the ribotypes of the isolates from a patient were identical after digestion with *Hind*III, the result was confirmed by ribotyping after digestion with *Eco*RI (Boehringer Mannheim) [39].

Statistics

A χ^2 test was used to assess the significance of differences between groups. Univariate logistic regression was used to evaluate the effect of the patient's characteristics (age and a history of UTI as independent variables) on the risk for recurrence (OR; 95% CI). Univariate logistic regression was also used to evaluate the effect of bacterial characteristics as independent variables on the presence of the same original strain as the causative agent in each recurrence.

Results

During the 12-month follow-up, 88 (49.2%) of the 179 women had at least one episode of UTI; altogether, 147 UTI

episodes were diagnosed. Of these episodes, most (138) were acute cystitis; only five episodes of acute pyelonephritis and four episodes of asymptomatic bacteriuria were diagnosed.

Of the 147 UTI episodes, 16 (10.9%) occurred within 1 month after the index episode (figure 1). Of these 16 episodes, five were classified as persistent infections, with a positive culture of the urinary sample 2 weeks after the index episode, and 11 were apparently early relapses, with a negative culture 2 weeks after the index episode. The remaining 131 episodes occurred at least 1 month after the index episode and were classified as recurrences (figure 1). The rate of occurrences was 0.73 episode per patient-year (0.061 episode per patient-month). This rate was only slightly higher during the first 2 months (0.084 episode per patient-year) than later (0.051 episode per patient-year). Seventy-nine (44.1%) of the 179 patients had at least one recurrence during the follow-up. Forty-six patients (25.7%) had only 1 recurrence, 23 (12.8%) had 2, 6 (3.4%) had 3, 2 (1.1%) had 4, 1 (0.06%) had 6, and 1 (0.06%) had 7 (figure 2).

The age distribution of the patients was bimodal; there was a cumulation of young women (peak number were 24 years old) and elderly women (peak number were 64 years old). Of the patients who were at least 55 years old, 53% had at least one recurrence during the follow-up, while only 36% of the younger patients had at least one recurrence during the follow-up ($P = .02$). In the older group, advancing age did not increase the risk for recurrence (OR, 1.0), and in the younger group, increasing age slightly diminished the risk for recurrence (OR, 0.95; 95% CI, 0.91, 0.99). Among the younger patients, the greatest risk was found for women who were between 25 and 29 years of age (data not shown). The 18 patients with mild predisposing factors for UTIs did not have more recurrences than did the other patients (data not shown).

Recurrences were more common if the patient had a history of UTI. Seventy-seven (47.5%) of the 162 patients with a

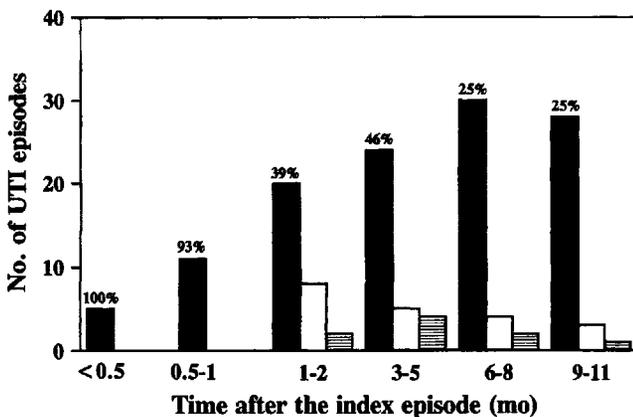


Figure 1. Number of episodes of urinary tract infection (UTI) caused by *Escherichia coli* (solid bars) or other bacteria (open bars) or culture-negative episodes (hatched bars) after the index episode. The percentage of *E. coli* isolates that were identified as the original strain is shown at the top of the bar.

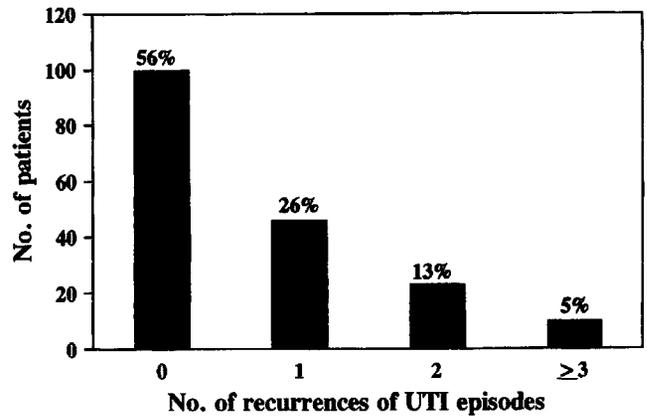


Figure 2. Number of recurrences of episodes of urinary tract infection (UTI) in 179 adult women who were followed up for 1 year after an index episode of community-acquired cystitis caused by *Escherichia coli*. 0 = no recurrence; 1 = one recurrence per patient; 2 = two recurrences per patient; ≥ 3 = three or more recurrences per patient. The percentage of women with the indicated number of episodes is shown at the top of the bar.

history of UTI had at least one recurrence during the follow-up, while only 2 (11.8%) of the 17 patients without previous UTI had at least one recurrence during the follow-up ($P = .004$); both of these women were older patients. In the group of younger patients, none of the 13 women without a history of UTI had recurrences during the follow-up ($P = .007$, younger women vs. elderly women). Univariate logistic regression revealed an odds ratio of 6.8 with a 95% confidence interval from 1.5 to 30.6 (analysis of all data).

Altogether, 118 (80%) of the 147 UTI episodes were caused by *E. coli*. Twenty episodes were caused by other bacteria (including *Klebsiella* species [9], *Staphylococcus saprophyticus* [3], enterococci [3], *Citrobacter* species [2], coagulase-negative staphylococci [1], *Enterobacter cloacae* [1], and *Morganella morganii* [1]), whereas cultures were negative in nine episodes despite typical clinical cystitis with pyuria.

The type of treatment (regimen) for the index episode did not have a statistically significant effect on the rate of recurrences. Forty percent of the patients who received therapy with trimethoprim or co-trimoxazole had at least one recurrence during the follow-up, while 52% of those who received nitrofurantoin or pivmesillinam had at least one recurrence during the follow-up ($P = .15$).

***E. coli* Strains Causing UTI During the Follow-up**

The following analysis of *E. coli* strains recovered during the follow-up included the 84 isolates available for typing. Seventy of these 84 isolates were recovered during true recurrences (i.e., episodes occurring at least 1 month after the index episode). The phenotype of all 84 strains was analyzed by O:K serotyping and assaying for hemolysin production and several

Table 1. Characteristics of *Escherichia coli* isolated during recurrences of UTI compared with those of *E. coli* isolated during index episodes of UTI.

The presence of indicated virulence-associated characteristic	Percentage of episodes per characteristic		
	Recurrences (n = 70)	Index episode with recurrences (n = 47)	Index episode without recurrences (n = 100)
P fimbriae	31	28	29
Non-P MR adhesins	13	19	21
Type 1C fimbriae	24	17	13
Hemolysin production	14	21	23
K5 or other K antigen (except K1)	54	45	45
O2, O8, or O75 antigen	14	15	17
VF2	60	51	52
VF3	30	26	25

NOTE. K = capsular; MR = mannose-resistant; O = somatic; UTI = urinary tract infection; VF2 = at least two virulence factors; VF3 = at least three virulence factors. No statistically significant differences were found between the groups.

adhesins. First, we examined whether the strains isolated during the recurrences were qualitatively different from those isolated during the index episode (table 1). No significant differences were found in regard to any of the characteristics previously shown to be epidemiologically associated with virulence [23, 24] (i.e., P fimbriae or non-P MR adhesins; type 1C fimbriae; hemolysin production; K5 or other K antigen except K1; and O2, O8, or O75 antigen). This finding was in fact not surprising since 90.5% of the index episodes had been recurrent episodes and only a small minority were first episodes. Table 1 also lists that the characteristics of the strains isolated during the index episode did not at all predict whether this episode would be followed by recurrences.

Next, we analyzed the strains isolated during the recurrences to determine whether these episodes were caused by the original strain isolated during the index episode. When phenotyping did not give an unequivocal identification (e.g., the strains were phenotypically noncapsulated, O nontypeable strains, or the strains belonged to the same O serogroup but seemed to differ in other respects), genomic ribotyping was performed. Altogether, 30 index episode strains and 37 recurrence strains were examined by this method.

As expected, all five strains isolated 2 weeks after the index episode and classified as representing persistent infection were identical to the original strain (figure 1). The same was true for eight (89%) of the nine strains isolated between 2 weeks and 1 month after the index episode; these strains represented early relapses.

Of the 70 *E. coli* strains isolated during recurrences, 39%–46% were identical to the original strains recovered 1–5 months after the index episode, as were 25% recovered during the two 3-month periods until the end of the follow-up (figure 1). Thus, during the whole follow-up period, one-third of all recurrences was caused by the original strain; of these recurrences, 57% occurred in the first 6 months after the index

episode. The rate of the recurrences due to the original strains was found to be approximately the same among younger patients and older patients (38% vs. 31%, respectively; $P = .54$). The type of treatment did not have a statistically significant effect on the quality of recurrence strains. Thirty-two percent of the recurrences in patients who received treatment with trimethoprim or co-trimoxazole and 34% of the recurrences in patients who received treatment with nitrofurantoin or pivmecillinam were caused by the original strain.

As a whole, many of the strains causing the index episodes of UTI probably persisted for a long time (even 1 year) in patients and caused new episodes from time to time. To see whether these persistent strains had some characteristics different from those of other *E. coli* strains, we compared the isolates recovered during the index episodes in the subgroup of 19 patients for whom the original strain was found to cause the recurrent episodes with those recovered from the 28 patients for whom there was no evidence of persistence of the original strain (table 2). Significant differences were found in the prevalence of MR adhesins (either P fimbriae or non-P MR adhesins), type 1C fimbriae, selected O and K antigens, and two or more virulence-associated characteristics. In each case, these characteristics were associated with persistence of the strains.

We then examined to what extent these characteristics would predict persistence by analyzing 70 recurrences by univariate logistic regression. We defined each of the virulence characteristics of the 70 index episode strains as independent variables and the presence of the original strain as the causative agent in each of the 70 recurrences (possibly indicating that the original strain had persisted in the body) as a dependent variable. The odds ratios with their 95% confidence intervals are listed in table 2. We found that if the original strain has MR adhesins or type 1C fimbriae or belongs to certain O or K groups, then it is probable that the recurrence strain will be the same strain with the same properties.

Table 2. Persistence of *Escherichia coli* strains in patients with recurrent UTI.

The presence of indicated virulence-associated characteristic*	Percent of recurrent episodes due to indicated strain per characteristic		OR (95% CI) [†]
	Original <i>E. coli</i> (n = 19)	New strain (n = 28)	
MR adhesins	63	36	4.4 (1.5, 13.0)
P fimbriae	37	21	2.8 (0.97, 8.4)
Non-P MR adhesins	26	14	2.4 (0.7, 8.5)
Type 1C fimbriae	32 [‡]	4 [‡]	4.4 (1.4, 13.9)
Hemolysin production	32	14	1.7 (0.5, 5.7)
K5 or other K antigen (except K1)	63	36	3.1 (1.1, 8.9)
O2, O8, or O75 antigen	26	7	4.7 (1.2, 18.2)
VF2	58 [§]	21 [§]	4.4 (1.5, 12.8)
VF3	42	7	6.3 (1.9, 20.5)

NOTE. K = capsular; MR = mannose-resistant; MR adhesins = P fimbriae or non-P MR adhesins; O = somatic; UTI = urinary tract infection; VF2 = at least two virulence factors; VF3 = at least three virulence factors.

* These characteristics were used as predictors of persistence, which was defined as the presence of the same original strain during each episode.

[†] Univariate logistic regression.

[‡] $P = .008$ (χ^2 analysis).

[§] $P = .01$ (χ^2 analysis).

^{||} $P = .004$ (χ^2 analysis).

Table 3 illustrates the different patterns of recurrences observed during the follow-up by a detailed description of the *E. coli* strains isolated from five patients. It also demonstrates the value of using multiple methods for typing. The information provided by genotyping (ribotyping) is further illustrated by figure 3.

Patient 1. The P-fimbriated, hemolysin-producing O6:K5 strain was the original strain. The first recurrence caused by a different strain (O4:K-) occurred 1 month after the index episode and was followed by an episode due to the original strain at 3 months and another episode due to a new strain (P-fimbriated rough:K1) at 9 months.

Patient 2. All five *E. coli* strains available for epidemiologic typing were phenotypically identical, noncapsulated, O nontypeable strains. However, ribotyping showed that only the first recurrence 1 month after the index episode was caused by the original strain (see also figure 3). Both of these first strains were also resistant to ampicillin, sulfonamide, and chloramphenicol, whereas the strains causing the following three recurrent episodes were susceptible to all antibiotics tested; their ribotyping patterns indicated that they each were different from the original strain and also from each other.

Patient 3. Each of the three episodes was caused by an O6 strain. However, the more-detailed phenotyping and genotyping showed that the two isolates recovered during the recurrent episodes were identical to each other but differed from the original strain (see also figure 3).

Patient 4. A P-fimbriated, type 1C-fimbriated O2:K7 strain caused five of the six recurrent episodes, whereas one recurrent episode was caused by a clearly different noncapsulated, O nontypeable strain; all of the strains were resistant to

sulfonamide, and the last three isolates were also resistant to trimethoprim. It is interesting that ribotyping showed some minor but repeatable variation between the O2:K7 strains isolated at different times, although the basic banding pattern (j:j) remained the same.

Patient 5. Four recurrences occurred during the follow-up. The first recurrence occurred 1.5 months after the index episode and was caused by the original strain (type 1C-fimbriated O25:K5 strain). Ribotyping revealed that the banding patterns (i) of these antibiotic-susceptible strains were identical to those of the O6:K5 strains isolated from patient 3 after digestion with *Hind*III but not with *Eco*RI. The strains causing the second recurrence (noncapsulated, O nontypeable strain) and the fourth recurrence (O nontypeable, K nontypeable strain) differed from each other by their antibiograms but were genotypically rather similar; these strains were defined as variants of each other.

Discussion

Only a few follow-up or long-term studies of women with uncomplicated recurrent UTI have been published [40-43]. In these studies, the patients were selected on the basis of their history of recurrent UTI. We describe here follow-up data for a nonselected group of 179 female outpatients; almost one-half (43%) of the women had a history of only sporadic or no UTI before the index episode. In addition, none of the women received antimicrobial prophylaxis during the follow-up, and only 18 patients had mild predisposing factors for UTI. Therefore, the women in the present study represent the female population seen by the general practitioner in Finland. The compliance of these 179 women during the whole study was excellent,

Table 3. Characteristics of the *Escherichia coli* strains isolated during index episodes and recurrences of UTI in five patients with epidemiologically interesting episodes during the follow-up period.

Patient no., time (mo) of episode/recurrence	Phenotype	Genotype*	Antibiotic resistance	Orig/New
1				
0 [†]	O6:K5:P+:Hly+	a:A	None	
1	O4:K-	b:B	None	New1
3	O6:K5:P+:Hly+	a:A	None	Orig
9	OR:K1:P+	c:C	None	New2
2				
0	ONT:K-	d:D	Amp, Sulfa, Chl	
1	ONT:K-	d:D	Amp, Sulfa, Chl	Orig
4	ONT:K-	e:E	None	New1
6.5	ONT:K-	f:F	None	New2
9	ONT:K-	g:G	None	New3
3				
0	O6:K-:NonP+:Hly+	h:H	None	
2	O6:K5	i:I	None	New1
3	O6:K5	i:I	None	New1
4				
0	O2:K7:P+:1C+	j:J	Sulfa	
1	O2:K7:P+:1C+	j:J	Sulfa	Orig
2	O2:K7:P+:1C+	j:J	Sulfa	Orig
3-4	<i>Klebsiella</i> × 3	ND	ND	ND
5.5	O2:K7:P+:1C+	j(var1):J(var1)	Sulfa, TMP	Orig (var1)
8	ONT:K-	k:K	Sulfa, TMP	New
9	O2:K7:P+:1C+	j(var2):J(var1)	Sulfa, TMP	Orig (var2)
5				
0	O25:K5:1C+	i:L	None	
1.5	O25:K5:1C+	i:L	None	Orig
5	ONT:K-	m:M	Sulfa, TMP, Tet, Nft	New1
8	O1:KNT	n:N	Sulfa, TMP, Tet, Nft, Amp, NA	New2
12	ONT:KNT	m(var):M(var)	Sulfa, Tet	New1 (var)

NOTE. Amp = ampicillin; 1C = type 1C fimbriae; Chl = chloramphenicol; Hly = hemolysin production; K = capsular; NA = nalidixic acid; ND = not determined; New = new stain; Nft = nitrofurantoin; NonP = non-P mannose-resistant adhesins; NT = nontypeable; O = somatic; Orig = original strain; P = P fimbriae; R = rough; Sulfa = sulfonamide; Tet = tetracycline; TMP = trimethoprim; UTI = urinary tract infection; var = variant; + = positive; - = negative.

* Determined after digestion with *Hind*III (small letters) and *Eco*RI (capital letters).

[†] Time of index episode.

thereby allowing the collection of all essential data during the 1-year follow-up period. Furthermore, during this period, there were 84 *E. coli* isolates from these patients that were available for detailed phenotypic and genotypic analysis. Thus, the study design provided reliable data about the recurrence of UTI in this group of women.

Ninety-four percent of the patients with UTI episodes during the follow-up presented with cystitis, which is consistent with the percentage (95%) of symptomatic patients in the study by Kraft and Stamey [42]. However, lower percentages of symptomatic patients have also been reported; in the long-term follow-up study by Stamm et al. [43], 73% of the patients were symptomatic. One explanation of these differences could be the varying criteria for patient contact during the follow-up. In addition to a few scheduled control visits, our patients were instructed to contact the community health center only when

they had symptoms of UTI, whereas in some other studies, the patients were seen in the clinic every 3 months irrespective of symptoms [43].

The ratio of cystitis-to-pyelonephritis episodes in the present study was 28:1, not unlike the ratio of 18:1 in the study by Stamm et al. [43]. The distribution of the causative agents of UTI during the follow-up did not differ from that found at the time of the index episode [23] or that found in previous studies [42]. Patient's age is well known as an important factor predisposing to bacteriuria, with the highest prevalence among the elderly [44-47]. Sanford [48] reported that only ~20% of women between 24 and 64 years of age had at least one episode of dysuria each year, most of which were caused by bacterial infection. In the present study, recurrence of UTI was more common in the women who were at least 55 years old than in the younger women, but in the group of elderly women, age

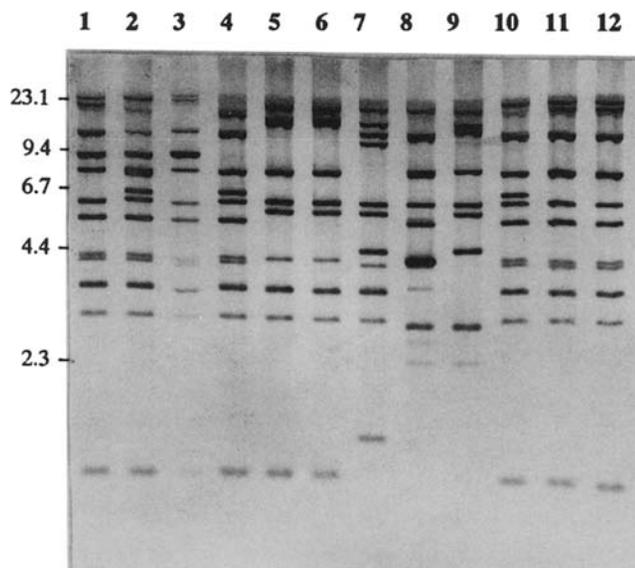


Figure 3. A schematic presentation of ribotypes of 12 *Escherichia coli* isolates from three patients (table 3, patients 1–3) with recurrences of urinary tract infection during the follow-up period. The numbers on the vertical axis represent the sizes (kilobases) of the respective hybridizing fragments. Lanes 1–4, isolates from patient 1; lanes 5–9, isolates from patient 2; lanes 10–12, isolates from patient 3.

did not seem to predispose to recurrence of UTI. Although the recurrences were less common in the group of women younger than 55 years of age as a whole, the rate of recurrence among the young women between 25 and 29 years of age was high. This higher rate is obviously due to the “honeymoon” phenomenon, although only five women had a clear-cut history of typical “honeymoon” cystitis. Sexual intercourse is evidently a predisposing factor for recurrence of UTI, as has been demonstrated in many previous studies [49–53].

At least one recurrence was detected in 44% of the patients during the follow-up, and the incidence rate was 0.73 recurrences per patient-year. This rate is somewhat less than the rates reported in most previous studies, probably because of the fact that in most follow-up studies the patients were specifically selected on the basis of a documented history of recurrent UTI [41–43]. The follow-up method (only spontaneous contact because of symptoms of UTI) also contributes to the lower rate of recurrence in the present study.

Of the 17 patients whose index episode of UTI was the first UTI in their life, two (11.8%) had at least one recurrence during the follow-up, while 79 (48.8%) of 162 women with a history of UTI had at least one recurrence during the follow-up. The incidence rates among women with and without a history of UTI were 0.18 and 0.89 episodes per patient-year, respectively. Both of the two women with their first UTI were old (68 and 70 years of age, respectively). These data clearly indicate that adult women with their first UTI have a very low risk of recurrence within the following year.

In this study we determined several phenotypic characteristics (O and K antigens, P and type 1C fimbriae, non-P MR adhesins, hemolysin production, and antibiogram) of the isolates. The comparison between isolates from a patient was also based on analysis of restriction fragment length polymorphism of rRNA genes from the isolates whenever the results of phenotyping were not unambiguous. Two restriction enzymes (*Hind*III and *Eco*RI) were used to increase the resolving power of ribotyping.

Using all these methods, we found that 67% of the recurrences of *E. coli* UTI were caused by a new strain, and the remaining 33% were caused by the original strain. Furthermore, the original strain could even cause a recurrence 11 months after the index episode, although the index episode of UTI was normally cleared and the urine culture was negative after the primary treatment. There could be an episode caused by a new strain between the index episode and a late relapse (table 3, patients 1 and 4).

In most previous studies, ~80%–90% of all recurrences were found to be reinfections caused by a new strain [1, 2, 52]. However, Brauner et al. [3], who followed up 23 women with index episodes of acute pyelonephritis, reported findings very similar to ours; one-third of the 49 recurrences observed were caused by the original strain. The original strain that caused pyelonephritis in one of their patients was isolated >6 months later from her urine (clinically asymptomatic bacteriuria); this episode occurred after two episodes caused by two different strains. In another patient, acute pyelonephritis was followed by cystitis caused by the identical strain 3 and 5 months later; between these episodes, the urine culture was negative.

One of the main goals of this study was to find out whether the virulence characteristics of the infective organism of the index episode would predict the risk of recurrence. There is no information on this topic in the published literature. Our results were very clear-cut in this respect and showed that expression of P fimbriae or other virulence factors (non-P MR adhesins, type 1C fimbriae, hemolysin, or certain K and O antigens) did not increase the risk of recurrence during the 1-year follow-up period (table 1).

On the other hand, it should be noted that the prevalence of these virulence factors among strains causing the recurrences was not lower than that among strains causing the index episodes and that this prevalence was higher than that among *E. coli* reservoirs in healthy persons studied previously [23, 32, 54]. Thus, the role of the virulence factors is as great a determinant of recurrences as of the first episodes of UTI. Furthermore, in those patients with recurrences, strains with these virulence factors persisted to a significantly greater extent than did strains without these factors (table 2). This finding suggests a new property associated with these factors, namely the ability to persist for long times (at least 1 year). The site of persistence was not determined in this study, but in the presence of clinical cure and sterile urine, the colon and vagina would be the most

likely reservoirs where antibiotic treatment could not eliminate the pathogen in all patients. The possibility also remains that the strain persisted in the spouse and that the UTI episode was due to reinfection from that source. Similar results have been reported by Wold et al. [4] and Tullus et al. [55] who found that strains with uropathogenic virulence factors were able to persist in the colon (an "infective reservoir").

As a whole, our results indicate that the same bacterial virulence factors identified as increasing the risk of UTI are also risk factors for recurrent UTI; our results also suggest that if treatment of UTI does not result in the elimination of the virulent strains from the body, then these strains tend to cause recurrences for a long time.

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