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Long-Term *Escherichia coli* Asymptomatic Bacteriuria among Women with Diabetes Mellitus

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Abstract

Background—Persistent *E. coli* asymptomatic bacteriuria (ASB) is common among persons with diabetes mellitus, but duration of colonization and re-colonization rates are unknown. We estimated duration of colonization and re-colonization among successively isolated *E. coli* from asymptomatic diabetic women and compared the virulence profiles to uropathogenic and commensal *E. coli*.

Methods—105 women with diabetes were enrolled in a randomized controlled clinical trial for treatment of ASB in Manitoba, Canada and followed at least every three months for up to three years. We analyzed 517 isolates from 70 women with repeated *E. coli* ASB for genetic similarity using ERIC-PCR. Unique strains were screened for uropathogenic virulence characteristics using dot blot hybridization, and compared to different collections of *E. coli* isolates.

Results—On average, there were differences between women assigned to treatment for ASB, those only treated for symptomatic infections and untreated women in: a) follow-up time with bacteriuria (29%, 31% and 66%, p=<0.001), b) duration of bacteriuria (2.2, 2.5 and 3.7 months, p=0.04) and c) carriage of unique isolates (2.4, 2.8 and 4 months, p=0.03). Women assigned to antibiotic treatment usually had recurrent infection (76%), 64% of the time with a genetically new *E. coli* strain. Virulence characteristics of these isolates were comparable to those of fecal isolates from healthy women.

Conclusions—Treatment may reduce the overall proportion of time infected in the long-term and carriage of a unique strain, but most treatment regimens were followed by subsequent re-colonization. Infecting strains did not have virulence factors characteristic of uropathogenic *E. coli*.

Keywords

urinary tract infection; diabetes; virulence; colonization; ERIC-PCR typing

INTRODUCTION

Urinary tract infections (UTI) occur in women with diabetes mellitus more frequently than in women without diabetes, are more severe, with pyelonephritis occurring at a five-fold higher

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We estimated duration of colonization and re-colonization among successively isolated E. coli from asymptomatic diabetic women and compared the virulence profiles to uropathogenic and commensal E. coli. Virulence factors of infecting strains were typical of commensal, not uropathogenic isolates.

rate, and often result in complications that are otherwise rare, such as emphysematous cystitis, and fungal infections [1,2]. Asymptomatic bacteriuria (ASB) occurs three times more often among women with diabetes than among otherwise healthy women; ASB is associated with an increased risk of symptomatic infection but is not causative [2–5]. The presence of ASB in diabetic women is not associated with a faster decline in renal function [6], or greater risk of diabetic complications or mortality[4]. The most common infecting organism in asymptomatic bacteriuric women with diabetes is *Escherichia coli*; other organisms include *Klebsiella spp.*, *Enterococcus spp.* and Group B *Streptococcus (S. agalactiae)* [2,7]. Uropathogenic *E. coli* (UPEC) have a variety of virulence traits that enable them to successfully invade the normally sterile urinary tract [8,9]. These include a number of adhesins, iron sequestration systems, and toxins which distinguish them from normal bowel flora *E. coli* [8].

Risk factors for ASB in diabetic women include sexual intercourse, degree of metabolic control, duration of diabetes, presence of diabetic complications, and insulin use [10–12]. In one study of symptomatic UTI among 589 women with diabetes, sexual intercourse in the preceding week was the most significant risk factor for women with Type I diabetes, whereas ASB was most significant for women with Type II diabetes [10]. Stringent control of blood glucose decreases risk of complications such as neuropathy and nephropathy, but a direct effect on bacteriuria has not been observed [1]. Neuropathy however, may affect underlying bladder dysfunction and thus contribute indirectly to a predisposition for UTI [1].

Although persistent *E. coli* ASB is more common in diabetics than in non-diabetics, it is unknown whether the bacteriuria is caused by the same *E. coli* strain, or what the effect of treatment is on the carriage of genetically similar or different *E. coli* strains. We conducted the present study to characterize urinary *E. coli* isolated from diabetic women in Manitoba, Canada, to determine if successive isolates from the same individual were genetically similar, and whether infecting organisms have a distribution of virulence genes similar to that of uropathogenic *E. coli* or to normal bowel flora *E. coli*.

METHODS

Patient Population

Diabetic women over the age of 16 were identified from 1991–1997 through ambulatory endocrinology clinics in Manitoba, Canada. 105 asymptomatic women with bacteriuria in two consecutive urine samples, obtained within a two week period, were enrolled into a prospective, randomized trial of antimicrobial or no antimicrobial treatment for ASB. Subsequently, urine specimens were obtained at least every 3 months, or more frequently after treatment or if symptoms occurred. Women were followed up to a maximum of 36 months. The original study was undertaken to determine whether there were any benefits with screening for and treatment of, ASB in diabetic women.

Women randomized to treatment received antimicrobial therapy for initial ASB, any subsequent ASB identified on 3 monthly screening, and any symptomatic infections. Women randomized to no treatment received treatment only for symptomatic urinary infection. All women received antimicrobials as ordered by their physicians for other indications. The trial design and patient population have been described in detail elsewhere [3].

We provide here further observations on *E. coli* isolates from a subgroup of 70 women who had at least two positive *E. coli* cultures during the study period. All *E. coli* isolates (517) from asymptomatic and symptomatic women in both study arms were typed for genetic similarity using ERIC–PCR. Genetically unique strains (238) from each individual were then analyzed for known UTI-associated virulence genes. We weighted data analyses for the length of follow-up time and interval between visits by assuming that ASB extended up to the midpoint between

visits on either side of each sample. We compared means using the student's t test and ANOVA, and used chi-square tests to compare the proportions of virulence genes between diabetic women and isolates from otherwise healthy women. This study was approved by the University of Manitoba Conjoint Ethics Committee for Human subjects.

Definitions

Asymptomatic *E. coli* bacteriuria was defined as urine specimens with an *E. coli* culture of $\geq 10^5$ CFU/ml colony forming units/milliliter of urine (cfu/ml) and no symptoms referral to the genitourinary tract. When symptoms consistent with infection were present, a urine specimen yielding an *E. coli* culture of $\geq 10^3$ cfu/ml was sufficient to diagnose urinary infection.

Recurrent infection was defined as a urine specimen growing *E. coli* after a subject received antimicrobial therapy (either for ASB, symptomatic UTI or other indications) or following spontaneous resolution of ASB. Recurrent infection was considered relapse when the strain of *E. coli* isolated following antimicrobial therapy was similar to the pre-therapy strain by ERIC-PCR typing, and reinfection when a new strain was isolated. Infection was considered persistent when additional urine specimens yielded *E. coli* cultures of $\geq 10^5$ cfu/ml among subjects who did not receive any antimicrobials for the duration of their follow-up period.

Molecular Typing

ERIC-PCR—Enterobacterial repetitive intergenic consensus (ERIC) sequences are highly conserved sequences found in intergenic regions of the genome in *Enterobacteriaceae*, but whose chromosomal location differs between species [13]. They are small in length (approximately 126 base pairs), and contain a central core inverted repeat. Although the function of these sequences is not fully known, amplification of these sequences by PCR allows clear distinction between different bacterial species and strains which contain these elements [13].

Briefly, cultures were grown overnight, lysed and the crude DNA lysate used for PCR under the following conditions: 94°C for 2 minutes, followed by 35 cycles of: 94°C for 30 seconds, 60°C for 1 minute, and 72°C for 4.5 minutes, with a 1 minute final extension at 72°C, using the ERIC primer: AAGTAAGTGACTGGGGTGAGCG in a thermal cycler (DNA Engine PTC-200, MJ Research, Inc.). UPEC sequenced strain *E. coli* CFT073 was used as a positive control. Samples were resolved on a 2% agarose gel (Figure 1).

The presence of a same size band of a similar intensity, identified using BioNumerics software (Applied Maths Inc., Austin, Texas), was used to compare isolates and create a dendogram using the unweighted pair group method with arithmetic averages (Figure 2). Strains were considered identical if they had 90% or greater similarity. Laboratory analyses were completed before clinical linkages between isolates were considered.

Dot Blot Hybridization—Briefly, dot blot hybridization involves fixing crude genomic DNA from each isolate on a nylon membrane using a Bio-Dot Microfiltration apparatus (Bio-Rad Laboratories, Hercules, CA). Fixed DNA were hybridized with a fluorescent labeled probe, the presence of which was detected using a fluorescein based system using the Amersham prime labeling and ECF detection system (Amersham, Arlington Heights, IL). A STORM 860 Phosphor Imager (Molecular Dynamics, Sunnyvale, CA) was used to scan the membranes to capture signal intensity of the image. The image was then analyzed using ImageQuant 5.2 software (Molecular Dynamics, Sunnyvale, CA). The signal of each isolate on the blot was expressed as a percentage of its respective positive control for each probe, after correcting for background signal [14]. Each isolate was tested in duplicate on independent

membranes and any discrepancy found in a particular isolate was retested using either another dot blot or southern blot hybridization.

We tested 238 unique *E. coli* isolates from 70 women for the presence of the following virulence genes associated with UTI using dot blot hybridization: the P pili family (*pap*F), its subclasses $papG_{J96}$, $papG_{AD}$, $prsG_{J96}$, S fimbriae (*sfa*), the Dr family of adhesins *drb*, cytotoxic necrotizing factor 1 (*cnf1*), hemolysin (*hly*), aerobactin (*iucD*), Group II capsule (*kps*MT) and outer membrane protease T (*omp*T). Virulence genes in the isolates from diabetic women were compared to previously published distributions among isolates collected from otherwise healthy Michigan women with a first UTI and recurring UTI, and periurethral and fecal isolates from healthy Michigan women [15].

RESULTS

The median age of the 70 women with *E. coli* ASB included in this analysis was 54 years (interquartile range (IQR): 43–64 years). Twelve women (17%) had bladder neuropathy, and 11/70 (16%) had prior genitourinary surgery. Overall, women had ASB for 36% of their follow-up time, with an average duration of bacteriuria of 2.6 months, and carried a unique single strain an average of 2.8 months (range: 0.6–13). Seventeen of the 68 (25%) women followed for six months or longer remained continuously colonized with a single strain for at least a six month period.

Of the 70 women, 36 were originally randomized to receive treatment and 34 to no treatment. Among the 34 women originally assigned to no treatment, 22 received treatment for symptomatic urinary infection or other indications at least once during the study period, and are referred to as women who received “symptomatic” treatment. Twelve women received no treatment for symptomatic UTI or other infections for the duration of their follow-up. Three of these 12 women had spontaneous resolution of *E. coli* ASB; one of whom was subsequently reinfected.

Women with either bladder neuropathy, prior genitourinary surgery, or both (N=20), had bacteriuria for 43% of their follow-up time compared to 26% for women without those conditions, although the difference was not statistically significant (p=0.1). They also did not carry a single strain for longer (2.5 months vs. 2.4 months, p=0.9), or have a different mean duration of *E. coli* bacteriuria than women without these conditions (2.2 months and 2.0 months; p=0.8).

There were no statistically significant differences in mean follow-up time between women who received treatment for ASB, symptomatic treatment only or no treatment (Table 1). However, treatment groups varied significantly in the mean proportion of follow-up time with *E. coli* bacteriuria ($p<0.001$), the mean duration of bacteriuria (p=0.04), and the mean length of carriage of a single strain (p=0.03) (Table 1). Specifically, women in the treatment group had bacteriuria for a lower proportion of their follow-up time, had shorter durations of bacteriuria and carried a single unique isolate for less time as compared to women who did not receive treatment. Women who received symptomatic treatment had a statistically lower proportion of their follow-up time with bacteriuria, but were not statistically different from women with no treatment in their duration of bacteriuria and length of carriage of a unique isolate.

On average, women assigned to treatment for ASB, received more antimicrobial courses than women who received only symptomatic treatment (Table 1). Among the 57 treated women with complete data, the majority of treatment regimens among women in the treatment group (76%) were followed by recurrent *E. coli* bacteriuria, most (64%) with a new strain of *E. coli*. Women who received treatment only for symptomatic infections also had frequent recurrent bacteriuria (65%). However, most (57%) were relapses with a strain genetically

identical to the previous infecting strain. The differences between the two groups were not statistically significant, possibly due to small sample size.

The frequency of uropathogenic virulence characteristics among isolates causing ASB in diabetic women were not statistically different from the frequency found among fecal *E. coli* in healthy women (Table 2), except for cytotoxic necrotizing factor 1, which was higher. Three virulence factors, *pff*, *kps*MT and *omp*T were found in significantly lower frequency than that seen in fecal strains.

DISCUSSION

This study demonstrates that untreated diabetic women with ASB may carry a genetically unique *E. coli* strain for up to 13 months, whereas treated women had more frequent acquisition of new strains. Women who received treatment for ASB had bacteriuria for a shorter duration and carried a single strain of *E. coli* for a shorter period of time as compared to women who did not receive treatment. However, treatment was followed by recurrent infections for the majority of women, usually with a new strain of *E. coli*. The ASB-causing *E. coli* from diabetic women did not have virulence characteristics typical of UTI-causing strains.

Women in the treatment group received antimicrobial therapy an average of three times, but some received treatment up to 15 times over the course of the trial either for ASB, symptomatic infections or other indications. The high proportion of recurrent infections indicates that repeated treatment does not resolve asymptomatic bladder infection over the long-term for the majority of diabetic women who have frequent *E. coli* ASB. These findings are consistent with the results of the clinical trial from which patients in this analysis were selected, showing a much higher frequency of recurrent ASB in women who received treatment for ASB [3].

Whereas treated women had shorter time with bacteriuria but frequent reinfections, untreated, diabetic, asymptomatic bacteriuric women carried a single strain for longer periods of time with eventual clearance in a minority of patients. In a study of otherwise healthy women with ASB, less than 1% of women had ASB lasting for longer than 2 consecutive monthly cultures, 26% percent were colonized with the same strain, and persistent infection with the same strain over time was uncommon [16]. In contrast, our data from diabetic women with ASB showed long-term carriage of the same strain of *E. coli* over time (25% of women carried the same strain for at least a six-month period), and whether they received treatment or not, the majority had recurrent asymptomatic infections, symptomatic infections, or both. Interestingly, diabetic, asymptomatic bacteriuric women with conditions predisposing them to UTI (bladder neuropathy or prior genitourinary surgery), did not differ from ASB diabetic women without those conditions in the proportion of time that they were infected, the length of carriage of a single strain, or the average duration of a bacteriuric episode. The reason for this is unclear and may be a result of the small number of women in these groups, but warrants further research.

In uncomplicated UTI, infecting *E. coli* have a number of virulence factors that assist in their colonization of the urinary tract including a variety of adhesins, iron sequestration systems, and toxins [8]. Most of the published literature on ASB causing *E. coli* indicates that these strains are less virulent [17–19]. Recent molecular studies demonstrate that some ASB causing *E. coli* strains are non-virulent commensal strains, whereas others were originally virulent strains which have evolved to commensalism [20,21]. We show that virulence characteristics of isolates from diabetic women with ASB were not different from those seen in fecal isolates. This low prevalence of virulence characteristics is consistent with previous reports among otherwise healthy individuals [22] and among diabetic women with ASB as compared to diabetic women with symptomatic UTI [23]. Only cytotoxic necrotizing factor 1 was found more frequently than in fecal *E. coli*, the presence of which has been associated with a decline

in renal function in diabetic women [23]. Moreover, three virulence genes, *pff*, *omp*T and *kps*MT, occurred at a significantly lower frequency than observed in our collection of fecal *E. coli* from healthy young women. These data combined with the strain carriage patterns that were observed, indicate that virulence characteristics typically found in UPEC are uncommon among isolates that infect the urinary tract in diabetic women with ASB. Thus, normal bowel inhabitants which do not invade the urinary tract under normal circumstances, may be capable of doing so in diabetic women, and can persist for long periods of time.

There are several limitations in this analysis. The ERIC-PCR technique has a degree of variability in the banding pattern intensity seen in strains. By running a variable control in each run, and by running large batches of isolates together, we attempted to minimize this variation. Most isolates from an individual were run in the same batch. Additionally, individuals may carry multiple *E. coli* strains, but the strain collection techniques only allowed for the collection of the predominant, morphologically distinct strain for genetic analysis. This could have resulted in an underestimation of strain turnover. Molecular typing and dot blot hybridization may not account for minor mutations arising in isolates over the long term. However, the small proportion of isolates in which this could have occurred is unlikely to have influenced the current analyses.

Our analyses of diabetic women with long-term ASB show that a diverse group of *E. coli* strains are capable of long-term urinary colonization in diabetic women. Recurrent infections were common after treatment, frequently with a new *E. coli* strain. The proportion of strains with UTI virulence characteristics was not significantly different from that seen in fecal strains from healthy women, indicating that in a predisposed host, additional bacterial aids for initiating infection are not a necessity.

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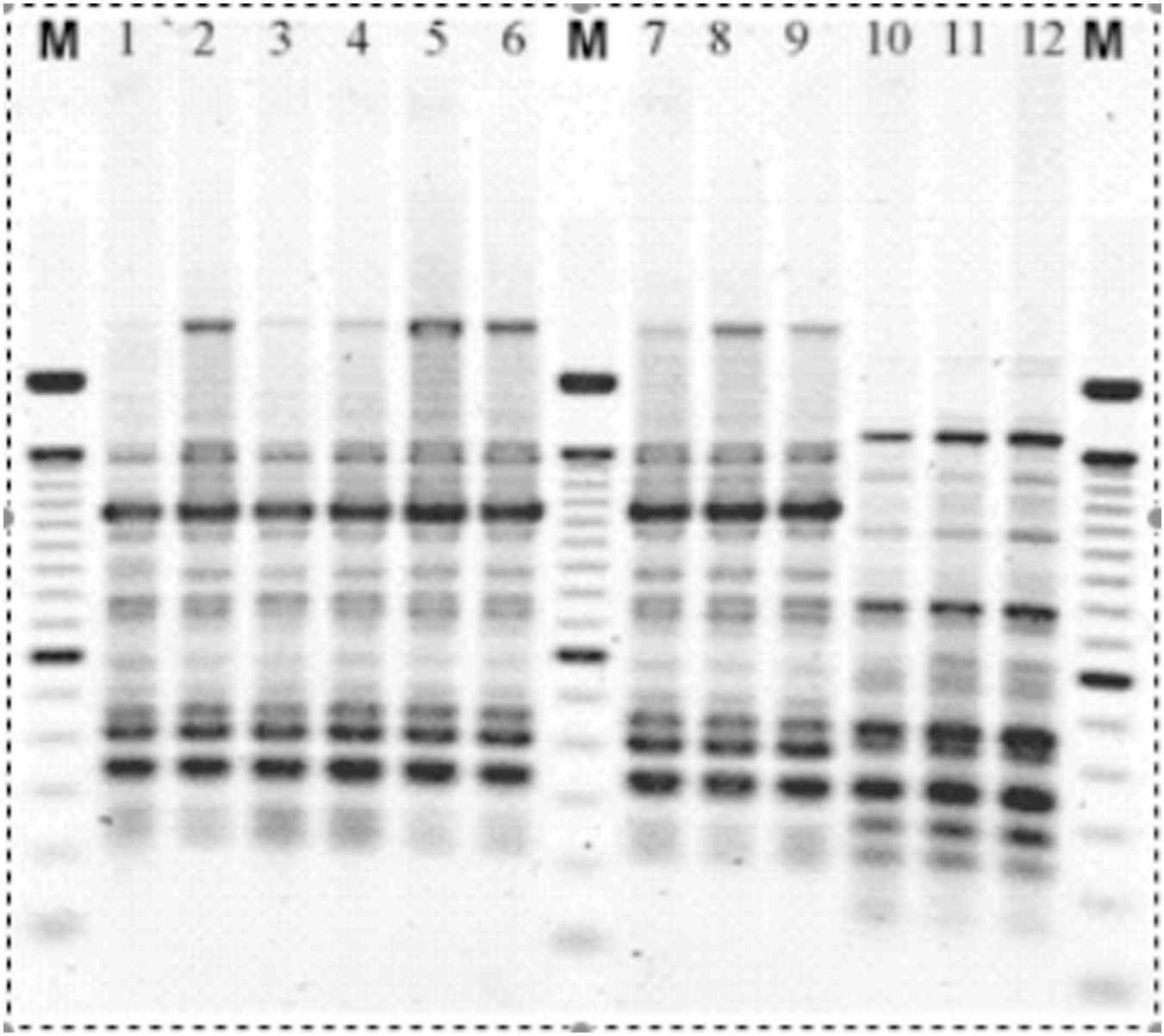

Figure 1.
Agarose gel of ERIC-PCR patterns from *E. coli*. Lanes marked M contain a molecular weight marker. Lanes 1-9 are isolates from one individual. Lanes 10–12 are from a different woman.

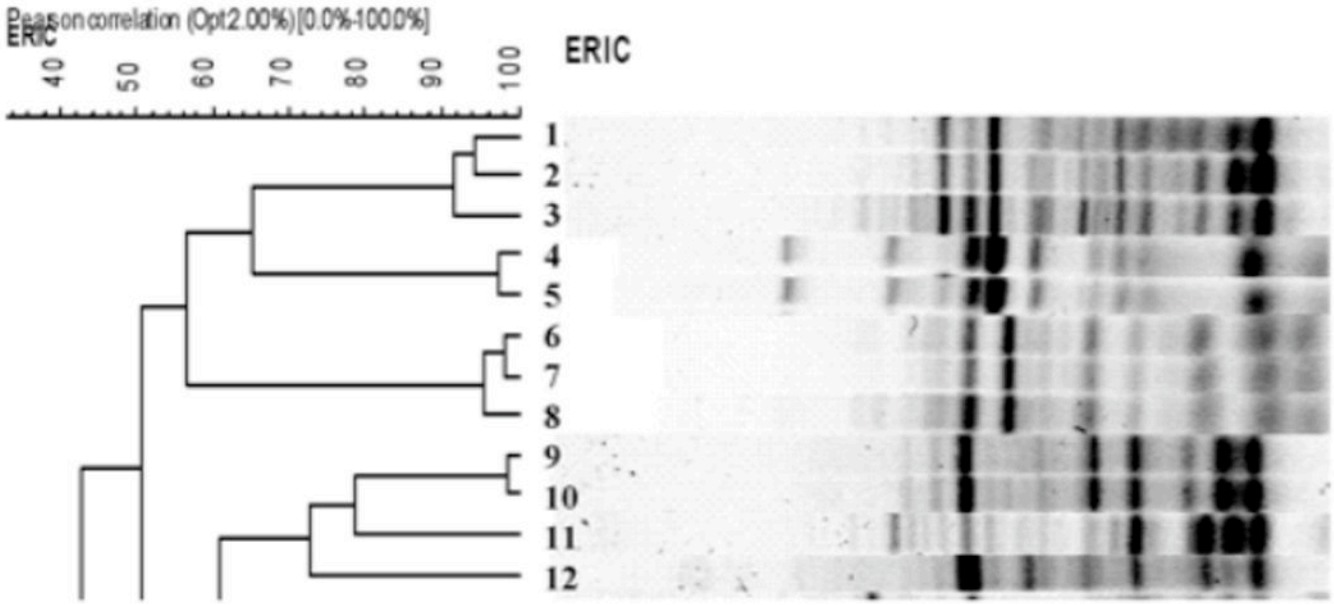

Figure 2.
Dendogram showing grouping of isolates according to similarity in banding pattern of samples from 5 women using the unweighted pair group method with arithmetic averages (UPGMA) of BioNumerics software. Lanes 1–3 are samples from person 1, lane 4 from person 2, lane 5 from person 3, lanes 6, 7, 8 from person 4 and lanes 9–12 from the fifth person. ERIC: enterobacterial repetitive intergenic consensus sequence.

Table 1

E. coli bacteriuria, strain carriage, and recurrent infection among diabetic women with asymptomatic bacteriuria by treatment received.

	Treatment* N=36	Symptomatic treatment* N=22	No treatment* N=12	p-value
Mean person-months of follow-up (IQR)	26 (18–36)	29 (20–36)	27 (17–36)	0.74
Mean proportion of follow-up time with bacteriuria (IQR)	0.29 (0.09–0.40)	0.31 (0.16–0.40)	0.66 (0.46–0.91)	<0.001
Mean duration of bacteriuria in months (IQR)	2.2 (1.6–2.9)	2.5 (1.8–3.1)	3.7 (1.31–5.4)	0.04
Mean length of carriage of a single strain in months (IQR)	2.4 (1.6–2.8)	2.8 (2.1–3.2)	4 (1.6–6.6)	0.03
Mean number of times received treatment (IQR)	3.2 (1–4)	2.0 (1–3)	--	0.05
Mean proportion of treatment courses followed by recurrent *E. coli* (IQR)	0.76 (0.67–1)	0.65 (0.5–1)	--	0.18
Mean proportion of recurrence caused by reinfection** (IQR)	0.64 (0.25–1)	0.43 (0–1)	--	0.16

* "Treatment" indicates women originally randomized to treatment for asymptomatic bacteriuria (ASB). "Symptomatic treatment" indicates women originally randomized to no treatment for ASB, but who received antimicrobials for symptomatic urinary infections or other indications over the course of their follow-up. "No treatment" indicates women originally randomized to no treatment for ASB and who did not receive any antimicrobials for the duration of their follow-up.

** Reinfection is defined as recurrent *E. coli* that is genetically different from the pre-treatment strain.

Abbreviations: N=number of women, IQR = inter-quartile range.

Table 2

Comparison of the frequency of *E. coli* virulence genes seen in asymptomatic bacteriuric (ASB) diabetic women with *E. coli* isolates from various other collections.

	Percentage of *E. coli* strains harboring the gene					
Virulence Factor (Gene name)	**ASB Diabetic women, Age >16 yrs (n=238)**	**Fecal (no UTI) Age 18–39 yrs (n=269)**	**First UTI Age 18–39 yrs (n=237)**	**Recurring UTI Age 18–39 yrs (n=27)**	**UTI Age 40–65 yrs (n=87)**	**Periurethral Age 18–39 yrs (n=53)**
Dr family of adhesins (*drb*)	9.7	5.6	15.2	7.4	10.3	3.8
P-pili family (*pff*)	24.1	34.2	49.8	59.3	57.5	34.0
Class I, P-pili ($papG_{J96}$)	0.0	0.0	2.1	3.7	2.3	0.0
Class II, P-pili ($papG_{AD}$)	18.5	23.1	27.0	37.0	31.0	11.3
Class III, P-pili ($prsG_{J96}$)	11.1	8.6	21.1	29.6	24.1	20.8
S fimbriae (*sfa*)	18.5	12.6	27.9	44.4	41.4	24.5
Cytotoxic necrotizing factor 1 (*cnf* 1)	18.3	10.0	26.6	40.7	29.9	24.5
Hemolysin (*hly*)	18.3	14.9	37.6	48.2	44.8	26.4
Aerobactin (*aer*)	40.6	41.3	46.0	40.7	37.9	26.4
Outer membrane protease T (*omp*T)	31.4	67.7	83.1	85.2	88.5	75.5
Capsule, Group II (*kps*MT)	38.4	63.6	81.9	74.1	75.9	73.6

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