The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat?

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(See the Editorial Commentary by Wagenlehner and Naber, on pages 778–80.)

Background. Little is known about the role of asymptomatic bacteriuria (AB) treatment in young women affected by recurrent urinary tract infection (UTI). We aimed to evaluate the impact of AB treatment on the recurrence rate among young women affected by recurrent UTI.

Methods. A total of 673 consecutive asymptomatic young women with demonstrated bacteriuria from January 2005 to December 2009 were prospectively enrolled. Patients were split into 2 groups: not treated (group A, n = 312) and treated (group B, n = 361). Microbiological and clinical evaluations were performed at 3, 6, and 12 months. Quality of life was also measured. Recurrence-free rate at the end of the entire study period was the main outcome measure.

Results. At baseline, the 2 most commonly isolated pathogens were *Escherichia coli* (group A, 38.4%; group B, 39.3%) and *Enterococcus faecalis* (group A, 32.7%; group B, 33.2%). At the first follow-up visit, there was no difference between the 2 groups (relative risk [RR], 1.05; 95% confidence interval [CI], 1.01–1.10), whereas after 6 months, 23 (7.6%) in group A and 98 (29.7%) in group B showed recurrence with a statistically significant difference (RR, 1.31; 95% CI, 1.21–1.42; $P < .0001$). At the last follow-up, 41 (13.1%) in group A and 169 (46.8%) in group B showed recurrence (RR, 3.17; 95% CI, 2.55–3.90; $P < .0001$). One patient in group A and 2 patients in group B were found to have pyelonephritis.

Conclusions. This study shows that AB should not be treated in young women affected by UTI, suggesting it may play a protective role in preventing symptomatic recurrence.

Asymptomatic bacteriuria (AB), defined as the presence of bacteria in the urine of an individual without signs or symptoms of a urinary tract infection [1], is thought to be present in 3%–5% of young healthy women and is more common in patients with diabetes and elderly persons [2]. Even though AB appears to be associated with adverse outcomes in some groups, such as pyelonephritis or preterm delivery in pregnant women [3], little is known about its role among young women with recurrent urinary tract infections (UTIs). The role of treatment of AB in pregnant women for reducing the incidence of pyelonephritis and low-birthweight infants is well known [4]. On the other hand, only 1 good-quality clinical trial has been performed on nonpregnant women, with the evidence that the placebo group was no more likely than the treatment group to have a symptomatic UTI [5]. In everyday clinical practice, we sometimes note that young women affected by recurrent UTI showed, after a

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course of antibiotic treatment, an asymptomatic period associated with sterile urine and then an episode of AB. In the majority of cases, even if it is not recommended, AB is treated with poor results and occasionally can allow the development of selection of multidrug-resistant bacteria [6]. From this background, the questions are: Should AB be treated in women affected by recurrent UTI, after antibiotic treatment? Does AB play a protective role for preventing recurrence in women affected by UTI? This evidence should be important for health policy in terms of cost reduction and better antibiotic use strategy. However, to the best of our knowledge, no study on otherwise healthy women has yet been performed to evaluate the role of AB treatment in patients affected by recurrent UTI. Herein we evaluate the impact of the treatment of AB on the recurrence rate among young women affected by recurrent UTI.

MATERIALS AND METHODS

Study Design

All consecutive women with AB attending the same sexually transmitted disease (STD) center between January 2005 and December 2009 for recurrent UTIs were prospectively screened for this study. They underwent microbiological evaluation, even though asymptomatic, because it is routine practice in our STD centers for all subjects with recurrent UTI to undergo microbiological evaluation after antibiotic treatment as part of follow-up [7].

Inclusion and Exclusion Criteria

Women were eligible for inclusion if they were between 18 and 40 years of age, were sexually active, regularly had sexual intercourse, had a singular sexual partner during the last 12 months, and had at least 1 symptomatic UTI treated within the 12 months prior to the current AB episode [8] but were asymptomatic at enrollment and showing a urine culture with at least 10^5 colony-forming units (CFUs)/mL of uropathogens [1]. Women were excluded if they were pregnant, lactating, or in menopause; were affected by major concomitant diseases such as diabetes, liver, and/or renal failure; had known anatomical abnormalities or malignancy of the urinary tract, bladder, or upper tract stones, diverticula, foreign bodies, or chronic retention; had polycystic kidney disease or evidence of pyelonephritis (ie, temperature >38°C, severe back pain, or costovertebral angle tenderness); had neutropenia <1000 cells/mL; or had acute cystitis symptoms, including dysuria, frequency, or urgency. Women who had recently (<4 weeks) been administered oral, parental, or vaginal topical antimicrobial agents or who were currently using prophylactic antibiotic drugs and who had vaginitis or cervicitis of any etiology were also excluded, as were women with indwelling catheters or those who self-catheterized. Similarly, women who tested positive for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, or herpesvirus type 1 or type 2 (HSV 1 or 2) and human papillomavirus (HPV) were excluded. Only women positive for uropathogens at urinary culture were included. We considered as uropathogens the following bacteria: enteric gram-negative rods, enterococci, *Staphylococcus saprophyticus*, and group B streptococci [9]. Women with urine culture positive for multiple pathogens were excluded. Finally, all women who were about to start using a new method of contraception or who had started using a new method within 4 weeks before enrollment were also excluded. To enroll a homogeneous group of women, we considered for the analysis only women with the last symptomatic recurrent UTI episode at least 1 month prior to enrollment. Written informed consent was obtained from all patients before treatment. The study was conducted in accordance with good clinical practice guidelines with the ethical principles of the latest version of the Declaration of Helsinki.

Microbiological Considerations

AB was defined by the presence of at least 10^5 CFUs of uropathogen bacteria per milliliter in 2 consecutive voided urine specimens of a midstream urine specimen obtained from an asymptomatic woman on a routine scheduled visit [1]. Moreover, the diagnosis of AB in women is appropriate only if the same species is present in quantities of at least 100 000 CFUs/mL of urine in at least 2 consecutive voided specimens [1]. The presence or degree of pyuria has not, however, been shown to have prognostic significance and therefore was not considered [5, 10].

Study Schedule

After providing written informed consent, all eligible individuals completed a baseline questionnaire, underwent urological examination, and provided 2 clean-catch midstream urine samples collected over consecutive days. In accordance with Hooton et al, both samples had to be positive to qualify as AB. Patients who met the inclusion criteria were randomly assigned to 2 groups: not treated (group A) or treated (group B). All patients were assigned to groups in a 1:1 simple randomization according to a computer-generated schedule produced by the Department of Public Health and Epidemiology, University of Florence. No patients in group A underwent treatment. However, all episodes of symptomatic UTI were recorded and treated with antibiotics, depending on the organism and its susceptibility profile. All patients found to be positive by microbiological evaluation were censored. All patients in group B were treated with antibiotic therapy in accordance with antibiogram. The standard duration of therapy was in accordance with the types of antibiotics used. This is a

nonblinded study because group A patients did not receive placebo. All patients were scheduled for follow-up visits and microbiological analysis at 3, 6, and 12 months from enrollment, regardless of the reported symptoms. If the symptomatic recurrence occurred in the intervals between enrollment and the scheduled follow-up visits, women were asked to contact their STD center and to undergo microbiological testing. The principal measure of outcome was recurrence-free rate at the end of the study period.

Sample Collection and Laboratory Procedures

All samples were collected during urological examination at room temperature and immediately taken to the laboratory under refrigerated conditions. All urine samples were analyzed for cultures and aliquot for DNA extraction and polymerase chain reaction (PCR) for *C. trachomatis*, *N. gonorrhoeae*, HSV 1/2, and HPV detection. All urine samples were also used to measure leukocyte esterase and nitrite levels with a dipstick assay (Bayer Multistik Pro Reagent Strips) [11]. All subjects included in the study underwent urinary culture for common bacteria, yeasts, and urogenital mycoplasmata. Microbiological culture was carried out in accordance with the methods described by Hooton et al [12]. Urine DNA extraction and purification were performed by means of DNeasy1 Tissue Kit (Qiagen, Spa, Italy), as described by Mazzoli et al [13]. The *C. trachomatis* chromosomal DNA PCR procedure amplifying an *omp1* gene sequence was performed on 10 mL of the sample extraction mixture according to the procedure described by Pannekoek et al [14]. Our STD laboratory is registered for United Kingdom National External Quality Assessment for the molecular detection of *C. trachomatis*. The presence of both genital HSV types was investigated in urine of the entire patient population using Alpha Watch HSV 1/2 (Alphagenics Diaco Biotechnologies, Trieste, Italy) and HSV 1/2 Genotype TechPlate (Diatech, Trieste, Italy) [13]. Alpha Watch HPV (Alphagenics Diaco Biotechnologies) was used to investigate the presence of genital HPV in urine [13].

Questionnaires and Urological Visits

Patient quality of life was measured using an Italian version of the Quality of Well-Being, a validated, multiattribute health scale [15]. This scale was selected because it has been successfully applied to acute illnesses, whereas other quality of life scales, such as the SF-36 Health Survey, are more suitable for chronic conditions [16].

Statistical Analysis

To analyze the homogeneity of the 2 groups, the baseline characteristics were compared using the *t* test and Wilcoxon–Mann-Whitney test for continuous variables and by the χ^2 test for categorical variables (Mantel-Haenszel test). As the null hypothesis, we assumed that there was no difference among the groups in terms of recurrence rate. In order to determine how many people we need to enroll for getting results that reflect the our STD center target population as precisely as needed, the sample size was calculated prospectively under the following conditions: population size of women who annually attend our clinic for recurrent UTI (n = 3500), confidence

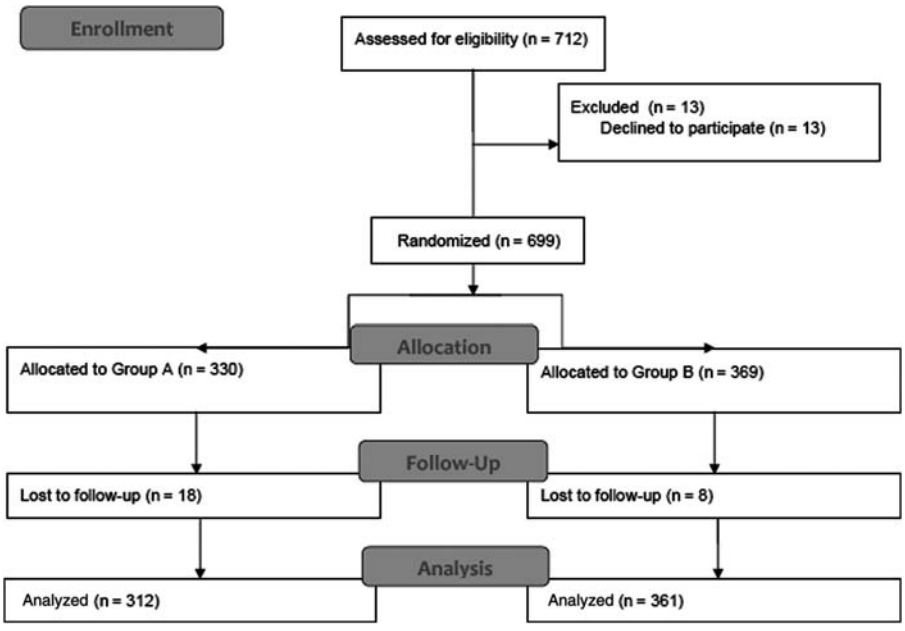

Figure 1. Study schedule according to the Consolidated Standards of Reporting Trials (CONSORT) group recommendations.

level = 99%, α error level = .05 (2-sided), and women who show AB = about 5%. The calculation yielded 558 individuals. Moreover, a share of 20% of women lost to follow-up was also considered. Fisher exact test and χ^2 test were used to assess the significance of all parameters, with $P < .05$ considered significant. Relative risks (RRs) were computed from the odds ratios using the Zhang-Yu method [17, 18]. Kaplan-Meier survival curves and the log-rank test were also used to evaluate the rate of probability of developing recurrence. The 95% confidence intervals (CIs) were calculated for the probability of survival for Kaplan-Meier estimates. Multivariate relative risk was calculated by using Cox proportional hazards regression. $P < .05$ was considered statistically significant. All reported P values were 2-sided. Statistical analyses were performed using SPSS 11.0 for Apple-Macintosh (IBM SPSS, Chicago, Illinois).

RESULTS

A total of 712 women with AB were screened; 13 were excluded because they rejected the protocol, and 699 were enrolled. Three hundred thirty women were assigned to group A (not treated) and 369 to group B (treated). Twenty-six patients were lost to follow-up; therefore, a total of 673 patients were analyzed (group A, 312; group B, 361) (Figure 1).

Baseline Results

The mean times of the symptomatic event and subsequent asymptomatic event were 6.3 months in group A and 5.8 in group B. No difference in clinical or microbiological parameters between the 2 groups at baseline evaluation was reported. All clinical, laboratory, and microbiological results are shown in Table 1. In group B, the most commonly used antibiotics were fosfomycin-trometamol (31.4%), nitrofurantoin (26.8%), co-trimoxazole (19.8%), ciprofloxacin (13.1%), and levofloxacin (8.9%).

Follow-up Results

Three months after enrollment, 11 (3.5%) patients in group A and 32 (8.8%) in group B showed clinical symptoms related to UTI and then underwent specific antibiotic therapy and were censored. Among all censored patients, isolated bacteria were as follows: group A (n = 11), 10 *E. coli* and 1 *Klebsiella* spp; group B (n = 32), 22 *E. coli*, 8 *Klebsiella* spp, and 2 *Enterococcus faecium*. No significant difference was reported between the 2 groups (RR, 1.05; 95% CI, 1.01–1.10; $P = .051$). The urine culture results from all patients who were not censored are shown in Table 2. At the second follow-up, 23 (7.6%) patients in group A and 98 (29.7%) in group B showed recurrence with a statistically significant difference (RR, 1.31; 95% CI, 1.21–1.42; $P < .0001$). In contrast, among all censored patients isolated pathogens were as follows: group A (n = 23), 19 *E. coli*, 1 *Enterococcus faecalis*, *and 3 Klebsiella* spp; group B (n = 98), 61 *E. coli*, 18 *Serratia* spp, 10 *Klebsiella* spp, 5 *Citrobacter* spp, and 4 *E. faecium*. All patients were treated in accordance with antibiogram results. Moreover, a statistically significant difference was reported in terms of quality of life questionnaire results ($t = 86.37$; $df = 628$; SE = 0.003; $P < .001$). Twelve months after enrollment, 41 (14.7%) patients in group A and 169 (73.1%) in group B showed recurrence. Among all censored patients, isolated pathogens were as follows: group A (n = 41): 21 *E. coli*, 3 *E. faecalis*, 10 *Klebsiella* spp, and 7 *E. faecium*; group B (n = 169): 101 *E. coli*, 24 *Serratia* spp, 19

Table 1. Patient Clinical and Laboratory Characteristics at Enrollment (N = 673)

Characteristic	Group A (n = 312)	Group B (n = 361)	*P* Value
Median age (±SD)	39.1 (6.9)	38.7 (7.1)	.77
Marital status			
Married	178 (57.0)	153 (42.3)	.26
Single	134 (43.0)	208 (57.7)	
Sexual encounters per week (±SD)	2.1 (1.3)	2.3 (1.4)	.05
Contraceptive use	141 (45.1)	157 (43.4)	.43
Oral hormonal	71/141 (50.3)	81/157 (51.5)	
Condom	37/141 (26.3)	48/157 (30.5)	
Coitus interruptus	33/141 (23.4)	28/157 (17.8)	
Smoking			
Yes	104 (33.3)	142 (39.3)	.10
Alcohol use			
Yes	61 (19.5)	77 (21.3)	.56
Parity			
Nulliparity	63 (20.2)	96 (26.5)	.05
Multiparity	249 (79.8)	265 (73.5)	
Clinical presentation			
Asymptomatic	312 (100)	361 (100)	
No. of UTIs per year			
3	71 (22.7)	76 (21.0)	.59
>3	241 (77.3)	285 (79.0)	
Start of recurrent UTI history (mo)	20 ± 5.4	19 ± 5.1	.99
Symptoms score at baseline (mean)			
QoL	0.82 ± 0.03	0.81 ± 0.06	.99
Bacterial strains			
Escherichia coli	120 (38.4)	142 (39.3)	.95
Enterococcus faecalis	102 (32.7)	120 (33.2)	
Enterococcus faecium	38 (12.2)	47 (13.1)	
Klebsiella spp	19 (6.1)	22 (6.1)	
Streptococcus agalactiae	17 (5.5)	16 (4.5)	
Serratia spp	16 (5.1)	14 (3.8)	

Data in parentheses are No. (%) unless otherwise specified.

Abbreviations: QoL, quality of life; SD, standard deviation; UTI, urinary tract infection.

Table 2. Clinical and Microbiological Data at Each Follow-up Visit

	Follow-up Visit			
	Baseline (Enrollment)	First (3 months)	Second (6 months)	Third (12 months)
Group A				
Symptomatic	0	11	23	41
Asymptomatic	312	301	278	237
QoL score (±SD)	0.82 ± 0.03	0.79 ± 0.07	0.81 ± 0.06	0.82 ± 0.03
No bacterial growth	0	15 (4.9)	27 (9.7)	31 (13.1)
Escherichia coli	120 (38.4)	107 (35.7)	68 (24.4)	26 (11.0)
Enterococcus faecalis	102 (32.7)	101 (33.7)	149 (53.5)	177 (74.7)
Enteroccocus faecium	38 (12.2)	30 (10.0)	10 (3.5)	1 (0.4)
Klebsiella spp	19 (6.1)	18 (6.0)	9 (3.4)	…
Streptococcus agalactiae	17 (5.5)	15 (4.9)	7 (2.6)	…
Serratia spp	16 (5.1)	12 (3.9)	5 (1.7)	1 (0.4)
Proteus mirabilis	…	3 (0.9)	2 (0.8)	1 (0.4)
Pseudomonas spp	…	…	…	…
Citrobacter spp	…	…	1 (0.4)	…
Group B				
Symptomatic	0	32	98	169
Asymptomatic	361	329	231	62
QoL score	0.81 ± 0.06	0.50 ± 0.01	0.52 ± 0.01	0.51 ± 0.02
No bacterial growth	0	27 (8.2)	21 (9.0)	19 (30.7)
E. coli	142 (39.3)	131 (39.8)	142 (61.5)	17 (27.5)
E. faecalis	120 (33.2)	92 (27.9)	36 (15.6)	11 (17.8)
E. faecium	47 (13.1)	45 (13.6)	10 (4.3)	3 (4.8)
Klebsiella spp	22 (6.1)	19 (5.8)	6 (2.7)	…
Streptococcus agalactiae	16 (4.5)	8 (2.4)	5 (2.2)	…
Serratia spp	14 (3.8)	7 (2.3)	6 (2.7)	…
Proteus mirabilis	…	…	2 (0.8)	4 (6.4)
Pseudomonas spp	…	…	…	3 (4.8)
Citrobacter spp	…	…	3 (1.2)	5 (8.0)

Data are No. (%) unless otherwise specified.

Abbreviations: QoL, quality of life; SD, standard deviation.

Klebsiella spp, 15 *Citrobacter* spp, and 10 *Pseudomonas* spp. The 2 groups differed both in terms of recurrence rate (RR, 3.17; 95% CI, 2.55–3.90; $P < .0001$) and quality of life questionnaire results ($t = 134.20$; $df = 507$; SE = 0.002; $P < .001$). We note that in both group A and group B the prevalence of *E. coli* decreased over time, whereas the prevalence of *E. faecalis* increased gradually. However, only in group A was the difference in prevalence statistically significant ($t = 2678.64$; $df = 229$; SE = 0.002; $P < .001$) (Figure 2). Therefore, 1 patient in group A and 2 patients in group B were found to be affected by pyelonephritis and underwent antibiotic therapy, without any significant difference. Moreover, the Kaplan-Meier curve analysis showed that group B had a higher probability of developing recurrence in comparison with group A (RR, 2.14; SE = 0.187; $P = .003$) (Figure 3). Multivariate analysis showed that the use of antibiotic therapy ($P < .001$; hazard ratio [HR], 3.09; 95% CI, .19–4.20) and parity ($P = .03$; HR, 1.29; 95% CI, .61–1.99) were independent factors affecting the risk of developing a symptomatic UTI in our study population. Moreover, no patient reported any adverse event during antimicrobial therapy. Furthermore, we noted that at the second and third follow-up evaluations, the majority of patients who were recurrence-free were found to have asymptomatic bacteriuria from *E. faecalis* (Table 2). Finally, in group B no significant difference was reported between different antibiotic regimens and recurrence rate. However, these were not among the study aims.

DISCUSSION

Several studies suggested that AB is associated with an increased risk of developing a symptomatic urinary tract

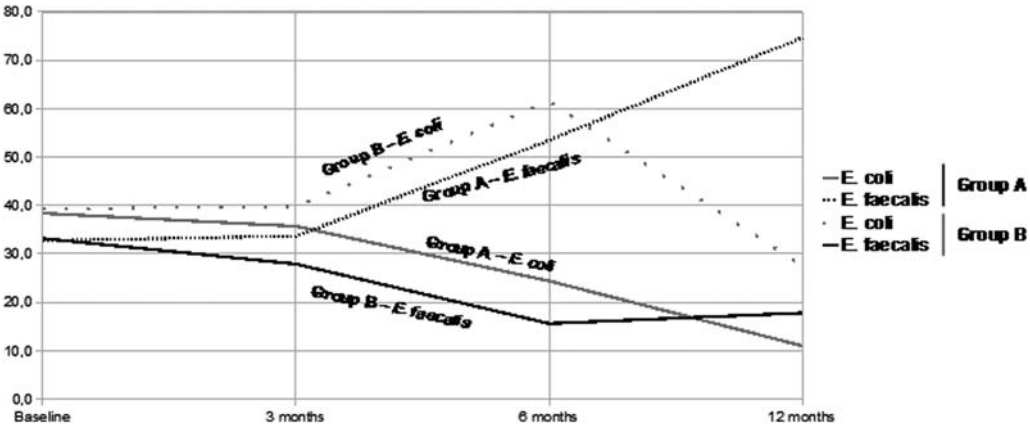

Figure 2. Prevalence of *Escherichia coli* and *Enterococcus faecalis* in the 2 study groups.

infection in an otherwise healthy population and in a specific category of subjects [1, 3, 19]. However, in those patients affected by recurrent UTI, the role of AB has never been evaluated. The present study shows 2 important fields to be discussed in order to facilitate the interpretation of findings. First, the treatment of AB in patients affected by recurrent UTI is associated with a higher rate of symptomatic UTI over 1 year. The second point to discuss is the modification of isolated bacteria after an antibiotic treatment. In particular, we noted that in cases of AB due to *E. faecalis*, a growth of multidrug-resistant *E. coli* could be found after a specific treatment, independent from the antibiotic chosen. Beerepoot et al reported an AB prevalence of 23.7% and 28.1% from *E. faecalis* and *E. coli*, respectively, in a group of premenopausal women affected by recurrent UTI [20]. Moreover, they demonstrated

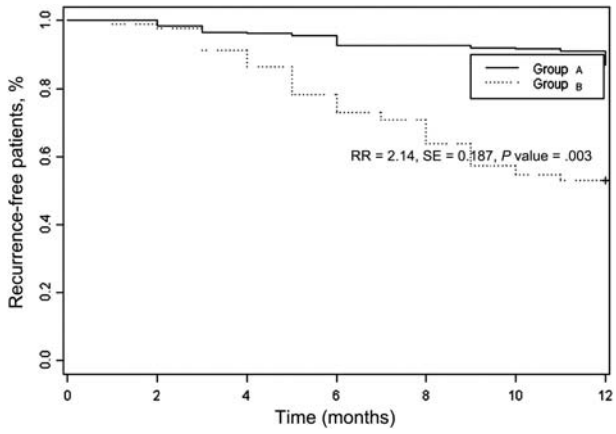

Figure 3. Kaplan-Meier curve analysis performed to calculate the probability of being recurrence-free between the 2 groups. Abbreviations: RR, relative risk; SE, standard error.

increased resistance rates for trimethoprim, amoxicillin, and ciprofloxacin in these *E. coli* isolates after 1 month in the trimethoprim/sulfamethoxazole group, but not in the control group [20]. Beerepoot et al's experiment demonstrated that oral administration of antibiotics for treatment of UTI can cause ecological disturbances in the normal intestinal microflora, promoting the emergence of antimicrobial-resistant strains [21]. Several authors demonstrated, in fact, that poorly absorbed antibiotic drugs can reach the colon in active form, suppress susceptible microorganisms, and disturb the ecological balance. Then, the suppression of the normal microflora may lead to reduced colonization resistance with subsequent overgrowth of preexisting, naturally resistant microorganisms, such as resistant potential pathogens that may spread within the body and cause severe infections [21]. The ecological effects of antibacterial agents on the human microflora should be the interpretative key of the negative effect of antibiotic therapy in women affected by recurrent UTI with AB. Winberg et al reported that several antibiotics disturb the normal vaginal microflora, reduce its adherence to vaginal epithelial cells in vivo, and promote a persistent vaginal *E. coli* colonization [22]. In addition, they demonstrated that amoxicillin also promotes the spread of *E. coli* from rectum to vagina, which may be of clinical significance [22]. Actually, the normal bacterial intestinal flora represents an important defense mechanism, which effectively interferes with the establishment of many important enteric pathogens [23]. It is well known that mechanisms by which microorganisms suppress the growth of other microorganisms include modification of bile acids, stimulation of peristalsis, induction of immunologic responses, depletion of essential substrates from the environment, competition for attachment sites, creation of restrictive physiologic environments, and elaboration of antibiotic-like substances [23]. Components of the intestinal

microbial flora also interact synergistically in the induction of disease or the utilization of substrate. In this sense, we can hypothesize that *E. faecalis* should be an important defense mechanism that effectively interferes with the establishment of many important enteric pathogens, such as *E. coli*. The last point to discuss is the high frequency of gram-positive bacteria found, as reported in our previous study [24]. This high frequency is likely due to the improved clinical use of fluoroquinolones for recurrent UTI patient treatment [25]. In their review, Colgan et al stated that a common dilemma in clinical medicine is whether to treat asymptomatic patients with bacteria in their urine [24]. Moreover, there are few scenarios in which antibiotic treatment of AB has been shown to improve patient outcomes, and Colgan et al identified specific categories in which treatment of AB is not recommended [26], without any reference to UTI patients. However, the present study shows a few limitations: (1) our study population is a specific population of patients attending an STD clinic; (2) we lacked a control group of healthy patients; and (3) this study population is a specific population of patients who had undergone multiple cycles of antibiotic therapy for recurrent UTI. However, we have enrolled a specific population of patients with recurrent UTI, who could represent a typical patient in general clinical practice. In conclusion, our results show that AB should not be treated when found in young women affected by recurrent UTI.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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