

## ANTIMICROBIAL TREATMENT IN DIABETIC WOMEN WITH ASYMPTOMATIC BACTERIURIA

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### ABSTRACT

**Background** Asymptomatic bacteriuria is common among women with diabetes, and the treatment of such infections has been recommended to prevent complications related to symptomatic urinary tract infection.

**Methods** We enrolled women (>16 years of age) with diabetes, bacteriuria ( $\geq 10^5$  colony-forming units of an organism per milliliter in cultures of two consecutive urine specimens), and no urinary symptoms; 50 were randomly assigned to receive placebo and 55 to receive antimicrobial therapy. For the first six weeks, which included the initial course of treatment, the study was placebo-controlled and double-blind. Subsequently, the women were screened for bacteriuria every three months for up to three years; antimicrobial therapy was provided to women in the antimicrobial-therapy group who had asymptomatic bacteriuria.

**Results** Four weeks after the end of the initial course of therapy, 78 percent of placebo recipients had bacteriuria, as compared with 20 percent of women who received antimicrobial agents ( $P < 0.001$ ). During a mean follow-up of 27 months, 20 of 50 women in the placebo group (40 percent) and 23 of 55 women in the antimicrobial-therapy group (42 percent) had at least one episode of symptomatic urinary tract infection. The time to a first symptomatic episode was similar in the placebo group and the antimicrobial-therapy group ( $P = 0.67$  by the log-rank test), as were the ( $\pm$ SD) rates of any symptomatic urinary tract infection ( $1.10 \pm 0.17$  and  $0.93 \pm 0.14$  per 1000 days of follow-up, respectively; relative risk, 1.19; 95 percent confidence interval, 0.28 to 1.81), pyelonephritis ( $0.28 \pm 0.08$  and  $0.13 \pm 0.05$  per 1000 days of follow-up; relative risk, 2.13; 95 percent confidence interval, 0.81 to 5.62), and hospitalization for urinary tract infection ( $0.10 \pm 0.36$  and  $0.06 \pm 0.22$  per 1000 days of follow-up; relative risk, 1.93; 95 percent confidence interval, 0.47 to 7.89). The women in the antimicrobial-therapy group had almost five times as many days of antibiotic use for urinary tract infection as did the women in the placebo group ( $158.2 \pm 1.7$  vs.  $33.7 \pm 0.91$  per 1000 days of follow-up; relative risk, 0.21; 95 percent confidence interval, 0.20 to 0.22).

**Conclusions** Treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications. Diabetes itself should not be an indication for screening for or treatment of asymptomatic bacteriuria. (N Engl J Med 2002;347:1576-83). Copyright © 2002 Massachusetts Medical Society.

URINARY tract infection is a common clinical problem in women with diabetes mellitus. Such women probably have a higher frequency of symptomatic infection than do women without diabetes,<sup>1</sup> and they also have more severe infections, with an increased risk of hospitalization for pyelonephritis<sup>2</sup> and a higher frequency of bacteremia<sup>3</sup> and bilateral renal involvement.<sup>4</sup> Serious, but uncommon, complications of urinary tract infection, including emphysematous cystitis<sup>5</sup> and pyelonephritis,<sup>6</sup> and intrarenal<sup>7</sup> and perinephric<sup>8</sup> abscess, occur primarily in patients with diabetes.

Asymptomatic bacteriuria is three times as common among women with diabetes as among women without this condition.<sup>9</sup> In the United States, some groups have recommended screening for and treatment of asymptomatic bacteriuria in women with diabetes.<sup>1,10</sup> This is not the standard of practice in Europe.<sup>11</sup> The identification and treatment of asymptomatic bacteriuria in nonpregnant women with diabetes would be appropriate if doing so prevented symptomatic infection, especially pyelonephritis or complications of urinary tract infection or diabetes. There are, however, no trials comparing treatment with nontreatment of bacteriuria in women with diabetes.<sup>12</sup> Therefore, we undertook this study to determine whether screening for and antimicrobial treatment of asymptomatic bacteriuria in women with diabetes decrease complications from urinary tract infection.

### METHODS

#### Study Design

This was a prospective, randomized trial comparing antimicrobial therapy with no antimicrobial therapy in diabetic women with asymptomatic bacteriuria who were followed for up to 36 months. For the first six weeks, the study was double-blind and placebo-controlled. Subsequently, both the participants and the study coordinator were aware of the treatment allocations. The study was approved by the University of Manitoba Conjoint Ethics Committee for Human Subjects, and written informed consent was obtained from all participants. All data were held and analyzed by the authors.

#### Enrollment of Patients

Women with diabetes were recruited from ambulatory endocrinology clinics at two tertiary care teaching hospitals and through

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community endocrinologists' offices. For the purposes of this study, women were defined as female subjects who were 17 years of age or older. Women were eligible for enrollment if they were older than 16 years, had two consecutive positive urine cultures ( $\geq 10^5$  colony-forming units [CFU] of an organism per milliliter) within a two-week period, and remained asymptomatic. Women who were pregnant, who had a serum creatinine level of more than 2.25 mg per deciliter (200  $\mu$ mol per liter), or who could not return for regular follow-up were excluded.

### Antimicrobial Therapy

At the start of the study, the women were randomly assigned to receive 3 or 14 days of antimicrobial therapy or placebo, according to a computer-generated list of random numbers. Because the first six women who were randomly assigned to three days' therapy all had an early relapse, this treatment group was discontinued. Treatment consisted of trimethoprim-sulfamethoxazole (160 mg and 800 mg, respectively, orally twice a day; Bactrim, Hoffmann-LaRoche) or matching placebo. Women who were allergic to trimethoprim-sulfamethoxazole or who were infected with resistant organisms received 250 mg of ciprofloxacin orally twice a day (Cipro, Bayer Canada) or corresponding placebo.

Symptomatic relapse or reinfection was managed in either group by administering progressively longer courses of therapy or long-term, low-dose antimicrobial prophylaxis. Prophylaxis usually consisted of trimethoprim-sulfamethoxazole (40 mg and 200 mg, respectively, three times weekly or 100 mg of trimethoprim at bedtime). Women in the antimicrobial-therapy group who had an asymptomatic relapse received four weeks of therapy after the first relapse and three months after the second. After a third relapse, a six-month course of antimicrobial suppression was offered. Asymptomatic reinfection was initially treated with a three-day regimen. If infection recurred two or more times within a six-month period, long-term (six months), low-dose antimicrobial prophylaxis was recommended.<sup>13,14</sup>

### Monitoring

At enrollment, the following data were collected for each woman: duration and complications of diabetes, all medications, ethnic origin (aboriginal or not), sexual-activity status, presence or absence of a urinary tract infection and a history of genitourinary surgery, and reproductive history. The clinical and microbiologic response of each woman was reviewed on days 3 and 14 of initial therapy and 2 and 4 weeks after the end of therapy. The women were then evaluated every three months or more frequently if symptoms occurred. At each visit, the women were questioned about symptomatic episodes, other infections, any antimicrobial agents received, and hospitalizations, and a urine specimen was obtained.

Quantification, identification, and susceptibility testing of organisms from urine cultures were performed according to standard methods.<sup>12</sup> A dipstick was used for urinalysis, and a hemocytometer was used to determine the urinary leukocyte count. At enrollment, the blood glucose level after an overnight fast, the glycosylated hemoglobin value, the blood urea nitrogen level, the serum creatinine level, and urinary protein and glucose levels were determined, and a complete blood count was obtained. These variables were not routinely monitored during the study, but the results of any subsequent tests performed as part of diabetes management were recorded.

### Definitions

Asymptomatic bacteriuria was defined by the finding of at least  $10^5$  CFU of the same organism per milliliter in cultures of two consecutive urine specimens in the absence of symptoms referable to the urinary tract.<sup>15</sup> Definite symptomatic lower urinary tract infection (acute cystitis) was defined by the acute onset of symptoms of

irritation of the lower tract, such as dysuria, urgency, and frequency, in the absence of fever or costovertebral-angle pain or tenderness, and in the presence of a positive urine culture ( $\geq 10^3$  CFU of a urinary pathogen per milliliter). Definite pyelonephritis was defined by the presence of costovertebral-angle pain or tenderness and a positive urine culture ( $\geq 10^4$  CFU of a urinary pathogen per milliliter) with or without systemic symptoms such as fever. An episode of symptomatic infection was considered probable if the woman had clinical symptoms compatible with the presence of a urinary tract infection and she had a response to antimicrobial therapy, but a urine culture was not available. A bacteriologic cure was defined by the absence of the recurrence of the pretherapy isolate four weeks after therapy. Reinfection was defined by the isolation of a new species or a new antimicrobial-susceptibility profile, and relapse by isolation of an organism similar to the pretherapy isolate within four weeks after the discontinuation of therapy. Further epidemiologic characterization of isolates was not performed.

### Statistical Analysis

To estimate the expected rate of symptomatic urinary infection in our study population and the number of subjects needed, we used the 4 percent rate of pyelonephritis reported in a study of 25 elderly women with asymptomatic bacteriuria.<sup>16</sup> During the 12-month study 28 percent of these women had a symptomatic infection, which included one episode of pyelonephritis (1 of 25, or 4 percent).<sup>16</sup> We estimated that the frequency of pyelonephritis among diabetic women with asymptomatic bacteriuria would be twice as high, or 8 percent per year, with a cumulative rate of 25 percent over a period of three years. If this rate was decreased to 5 percent by treatment, consistent with the decrease from 20 to 30 percent to 2 to 3 percent reported with treatment among pregnant women,<sup>17</sup> then 58 women would be needed in each group for the study to have 80 percent power to identify an absolute difference between groups of 20 percent with an  $\alpha$  level of 0.05.

The primary outcome variables were the time to the first episode of symptomatic urinary tract infection and the frequency of symptomatic urinary infection. Secondary outcomes included the response to the initial course of antimicrobial therapy, the occurrence of pyelonephritis, hospitalization for urinary tract infection, hospitalization for other causes, the total number of days of antimicrobial therapy, the occurrence of new episodes of asymptomatic bacteriuria, and adverse effects of antimicrobial agents for urinary tract infection.

The women's characteristics at enrollment were compared in the two study groups. Clinical and microbiologic outcomes related to the initial blinded, placebo-controlled treatment were compared 3, 14, 28, and 42 days after enrollment. We determined the incidence of various long-term outcomes per 1000 days, as well as the proportion of days on which antibiotics were given for urinary tract infections and the proportion of women who had treatment-related adverse effects. The time to the first symptomatic episode was measured from study enrollment to the onset of symptoms in the placebo group and from the end of initial antimicrobial therapy (i.e., day 15 after enrollment) to the onset of symptoms in the antimicrobial-therapy group.

All estimates are presented with two-tailed 95 percent confidence intervals. We compared categorical variables between groups using a chi-square analysis or Fisher's exact test; we used a t-test or repeated-measures analysis of variance for continuous variables. We used Mantel-Haenszel stratified analysis and logistic-regression analysis to adjust for concomitant factors. We used the method of Kaplan and Meier to estimate the time to the first symptomatic episode, followed by log-rank tests to evaluate differences between groups. We used Cox proportional-hazard modeling to adjust for concomitant factors. We used generalized estimating equations to compare rates of women with or without prophylaxis between groups. A P value of less than 0.05 was considered to indicate statistical significance, and all tests were two-tailed.

## RESULTS

## Enrollment of Patients

Cultures of initial urine specimens were positive in 268 of 1900 women with diabetes who were screened (14 percent). A second specimen was positive in 135 of 196 tested (69 percent). Between February 1991 and April 1997, 108 women were enrolled. Two women were lost to follow-up within one month after enrollment, and one was excluded after a complicated medical course prevented assessment of urinary outcomes. The final study cohort included 50 women who were randomly assigned to receive placebo and 55 who were randomly assigned to receive antimicrobial therapy. The characteristics of the two groups were similar at enrollment (Table 1).

## Short-Term Outcome

For the initial two-week course of therapy, 37 of 49 women (76 percent) received trimethoprim-sulfamethoxazole, and 12 (24 percent) ciprofloxacin. The results for six women who were randomly assigned to receive three days of antimicrobial therapy were excluded. Antimicrobial therapy led to a significantly higher rate of bacteriologic cure than did placebo at all short-term follow-up visits (Table 2). Infection recurred in 10 women in the antimicrobial-therapy group (20 percent). Ten women in the placebo group (20 percent) had resolution of bacteriuria, one of whom subsequently became reinfected, and three women (6 percent) became symptomatic and were treated, one of whom relapsed. Among the women in the placebo group, spontaneous resolution occurred in 6 of 13 women with gram-positive bacteriuria (46 percent) and 4 of 37 with gram-negative bacteriuria (11 percent) ( $P=0.01$  by Fisher's exact test).

## Long-Term Outcome

The mean duration of follow-up exceeded 2 years, and almost 50 percent of the women were followed up for 36 months (Table 3). The minimal duration of follow-up was two months in the antimicrobial-therapy group and four months in the placebo group. The reasons for withdrawal before 36 months of follow-up were as follows: deteriorating medical or functional status (nine women in the placebo group and seven in the antimicrobial-therapy group), moved from area (three and six, respectively), request of subject (four and nine, respectively), lost to follow-up (nine and four, respectively), death (one in each group), and pregnancy (one in the placebo group). Causes of death were congestive heart failure at 16 months and carcinoma of the colon at 31 months.

Overall, there were 65 definite and 5 probable episodes of cystitis and 14 definite and 3 probable episodes of pyelonephritis. The frequency of symptomatic

**TABLE 1. CHARACTERISTICS OF WOMEN WITH DIABETES WHO HAD ASYMPTOMATIC BACTERIURIA AT ENROLLMENT, ACCORDING TO WHETHER THEY RECEIVED ANTIMICROBIAL THERAPY OR PLACEBO.\***

CHARACTERISTIC	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=55)
Age — yr	57.0±11.15	53.7±11.8
Aboriginal ethnic origin — no. (%)	8 (16)	10 (18)
Sexually active — no. (%)	11 (22)	17 (31)
History of urinary tract infection — no. (%)	28 (56)	34 (62)
History of genitourinary surgery — no. (%)	12 (24)	14 (25)
Diabetes		
Type 2 — no. (%)	41 (82)	43 (78)
Duration — no. (%)		
<1 yr	8 (16)	10 (18)
1–5 yr	9 (18)	8 (15)
6–10 yr	14 (28)	10 (18)
11–20 yr	13 (26)	18 (33)
>20 yr	6 (12)	9 (16)
Complications — no. (%)		
Retinopathy	9 (18)	13 (24)
Neuropathy	11 (22)	14 (25)
Nephropathy	3 (6)	7 (13)
Blood glucose — no. (%)†		
<144 mg/dl	7 (15)	8 (15)
144–216 mg/dl	14 (29)	20 (36)
217–324 mg/dl	18 (38)	19 (35)
>324 mg/dl	9 (19)	8 (15)
Glycosylated hemoglobin — (%)	13.2±3.9	12.7±3.6
Serum creatinine — mg/dl‡	0.96±0.25	1.01±0.29
Glycosuria — no. (%)§	34 (68)	30 (55)
Proteinuria — no. (%)§	17 (34)	15 (27)
Urinary protein (semiquantitative) — g/liter	0.70±1.07	0.38±0.75
Urinary leukocytes — no./ml		
Median	40.5	44
Range	0–3360	0–1600
Infecting organisms — no. (%)¶		
<i>Escherichia coli</i>	31 (62)	33 (60)
<i>Klebsiella pneumoniae</i>	5 (10)	8 (15)
Other gram-negative bacilli	1 (2)	4 (7)
<i>Streptococcus agalactiae</i>	6 (12)	6 (11)
Other gram-positive organism**	7 (14)	4 (7)

\*Plus-minus values are means ±SD. There were no significant differences between groups.

†Results were available for 48 women in the placebo group. To convert values for blood glucose to millimoles per liter, multiply by 0.05551.

‡To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

§Glycosuria and proteinuria were defined as any level of glucose or protein, respectively, above a trace level on urinalysis.

¶Twelve gram-negative isolates (15 percent) were resistant to trimethoprim-sulfamethoxazole.

||*Proteus mirabilis* was isolated from two women, and *Citrobacter* species from three.

\*\**Gardnerella vaginalis* was isolated from three women, coagulase-negative staphylococcus from six, and *Enterococcus faecalis* from two; *G. vaginalis* was considered a gram-positive organism.

ASYMPTOMATIC BACTERIURIA IN DIABETIC WOMEN

**TABLE 2. SHORT-TERM MICROBIOLOGIC OUTCOMES AMONG WOMEN WITH DIABETES WHO HAD ASYMPTOMATIC BACTERIURIA, ACCORDING TO WHETHER THEY RECEIVED ANTIMICROBIAL THERAPY OR PLACEBO.\***

OUTCOME	DAY 3		DAY 14		DAY 28		DAY 42	
	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=49)	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=49)	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=49)	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=49)
	no. of women (%)							
Cure	4 (8)†	46 (94)	9 (18)†	48 (98)	10 (20)†	42 (86)	11 (22)†‡	39 (80)§
Treatment failure	46 (92)	1 (2)	41 (82)	0	39 (78)	0	37 (74)	0
Reinfection	0	2 (4)	0	1 (2)	0	3 (6)	1 (2)	6 (12)
Relapse	0	0	0	0	1 (2)	4 (8)	1 (2)§	4 (8)

\*Data on six women who were randomly assigned to receive three days of antimicrobial therapy were excluded.

†P<0.001 for the comparison of cure with other outcomes as compared with antimicrobial therapy.

‡Two women were treated for a symptomatic infection.

§One woman was treated for a symptomatic infection.

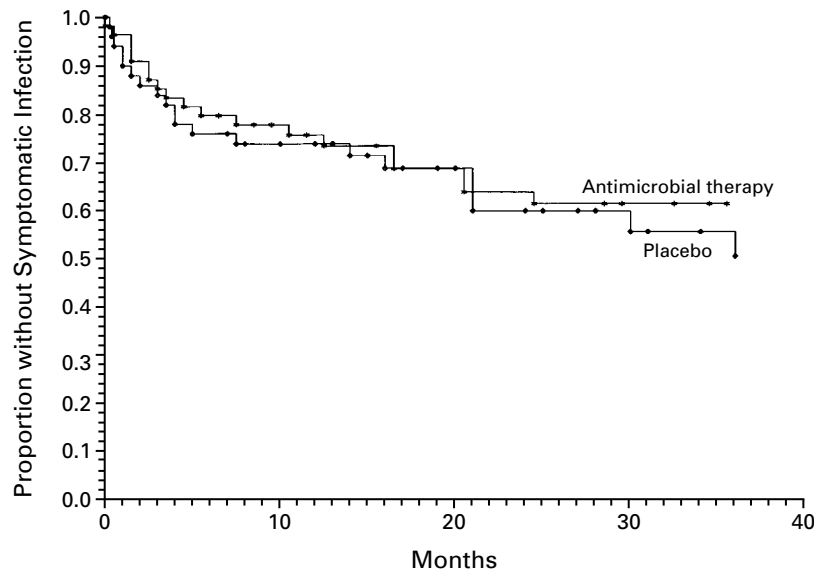
**TABLE 3. LONG-TERM OUTCOMES AMONG WOMEN WITH DIABETES ACCORDING TO WHETHER THEY RECEIVED ANTIMICROBIAL THERAPY OR PLACEBO FOR ASYMPTOMATIC BACTERIURIA.\***

VARIABLE	PLACEBO (N=50)	ANTIMICROBIAL THERAPY (N=55)	RELATIVE RISK (95% CI)	P VALUE
Follow-up				
Duration — days	796.7±334.3	840.3±325.8	—	
Duration — mo	26.2±11.0	27.6±10.7	1.05 (0.49–2.27)	0.51
36 Mo of follow-up — no. (%)	23 (46)	26 (47)	—	0.90
Episodes of symptomatic UTI — no./1000 days of follow-up (total no. of episodes)				
All episodes	1.10±0.17 (44)	0.93±0.14 (43)	1.19 (0.28–1.81)	0.42
Cystitis	0.83±0.14 (33)	0.80±0.13 (37)	1.03 (0.65–1.65)	0.89
Pyelonephritis	0.28±0.08 (11)	0.13±0.05 (6)	2.13 (0.81–5.62)	0.13
Days of antibiotic use/1000 days of follow-up				
Any antibiotic for a UTI	33.7±0.91	158.2±1.7	0.21 (0.20–0.22)	<0.001
Antibiotic for symptomatic UTI	10.9±0.55	8.26±0.42	1.31 (1.14–1.51)	<0.001
Antibiotic for asymptomatic UTI	0	30.1±0.79	—	<0.001
Prophylaxis or suppressive therapy	22.9±0.75	119.9±1.5	0.19 (0.18–0.20)	<0.001
Antibiotic for other infections	28.1±0.83	23.2±0.70	1.21 (1.11–1.31)	<0.001
Other outcomes				
Episodes of asymptomatic UTI — no./1000 days of follow-up (total no. of episodes)	0.53±0.12 (23)	1.43±0.18 (66)	0.37 (0.23–0.59)	<0.001
Episodes of asymptomatic UTI — no./1000 days of follow-up without antibiotic use	0.55±0.12	1.70±0.21	0.32 (0.20–0.51)	<0.001
Hospitalization for UTI — no./1000 days (total no. of episodes)	0.10±0.36 (5)	0.06±0.22 (3)	1.93 (0.47–7.89)	0.36
Hospitalization for other causes — no./1000 days of follow-up (total no. of episodes)	0.38±0.10 (15)	0.37±0.89 (17)	1.02 (0.51–2.05)	0.95
Treatment-related adverse effects — no. of women (%)	3 (6)	10 (18)	0.29 (0.07–1.11)	0.05

\*Plus-minus values are means ±SD. CI denotes confidence interval, and UTI urinary tract infection.

urinary tract infection (Table 3) and the time to the first symptomatic episode (P=0.67 by the log-rank test) (Fig. 1) were similar in the two groups. A majority of women in each group — 30 of 50 (60 percent) in the placebo group and 32 of 55 (58 percent) in the antimicrobial-therapy group — had no symptomatic episodes. Six (12 percent) and eight (15 percent) women, respectively, had only one symptomatic episode. The remaining 14 women in the placebo group (28 percent) and 15 women in the antimicrobial-therapy

group (27 percent) had 86 percent and 82 percent of all symptomatic episodes, respectively. One woman in the placebo group had three episodes of pyelonephritis, and eight women in this group each had one episode. Six women in the antimicrobial-therapy group had one episode of pyelonephritis each, and most of these episodes occurred during the first six months of the study (Fig. 2). Only two women in the placebo group had persistent bacteriuria from enrollment until pyelonephritis developed, at 1 and 11



**Figure 1.** Proportion of Women with Diabetes Who Remained Free of Symptomatic Urinary Tract Infection, According to Whether They Received Antimicrobial Therapy or Placebo at Enrollment.

There was no significant difference between groups in the time to the first symptomatic urinary tract infection ( $P=0.67$  by the log-rank test).

months (Fig. 2). Most women in the placebo group had received antibiotics for cystitis or other infections, including five women who had negative screening cultures for prolonged periods before pyelonephritis developed.

Women in the placebo group had significantly more days of antimicrobial therapy for symptomatic urinary tract infections and for other types of infections. Overall, however, women in the antimicrobial-therapy group had nearly five times the number of days of antimicrobial treatment (Table 3), a difference that was entirely attributable to the use of antibiotics for the management of asymptomatic bacteriuria. There were four hospitalizations and one overnight stay in the observation unit for urinary tract infection among four patients in the placebo group — four for pyelonephritis and one because of hematuria. Three women in the antimicrobial-therapy group were each hospitalized once for pyelonephritis. Two women in the antimicrobial-therapy group and one in the placebo group were hospitalized to control their blood glucose levels.

Women in the antimicrobial-therapy group had significantly more episodes of asymptomatic infection and more treatment-related adverse effects than did women in the placebo group (Table 3). Three of 15 women who underwent urologic evaluation (3 percent of all women) had urologic abnormalities identified: 1 woman in the placebo group had a urethral tumor resected at five months, and the woman in the

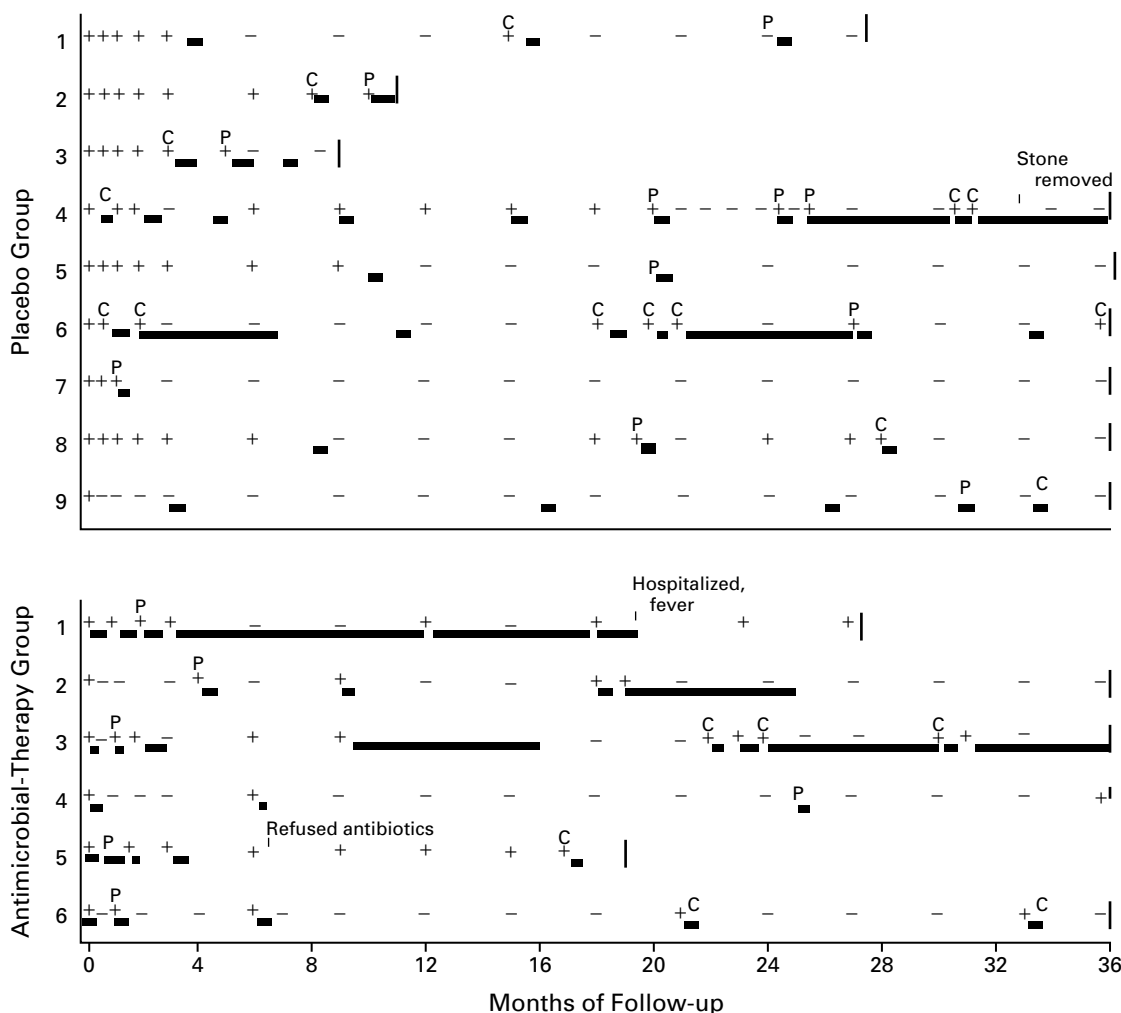
placebo group who had recurrent pyelonephritis had a renal stone, as did 1 woman in the antimicrobial-therapy group who had a relapsing *Proteus mirabilis* infection.

#### Metabolic Status and Diabetic Complications

At the end of the study, the mean ( $\pm$ SD) glycosylated hemoglobin values were similar in the women in the placebo group and the women in the antimicrobial-therapy group ( $10.4\pm 3.3$  percent [measured in 30 women] and  $10.1\pm 3.0$  percent [37 women], respectively;  $P=0.65$ ), as were the serum creatinine levels ( $0.93\pm 0.35$  mg per deciliter [ $82.0\pm 30.7$  mmol per liter] [36 women] and  $1.03\pm 0.41$  mg per deciliter [ $91.2\pm 35.9$  mmol per liter] [43 women], respectively;  $P=0.23$ ) and urinary protein levels ( $0.98\pm 1.32$  g per liter [50 women] and  $0.8\pm 1.24$  g per liter [55 women], respectively;  $P=0.47$ ). Two women in each group had clinically significant renal failure. Three of these patients had progression of diabetic nephropathy; the fourth had reversible renal failure that was attributed to drug-induced interstitial nephritis with concomitant acute pyelonephritis.

#### Associations with Symptomatic Infection

More than one symptomatic episode occurred in 13 of 28 women in the placebo group who had a history of urinary tract infection (46 percent), as compared with 1 of 22 with no prior history (5 percent) ( $P=0.001$ ). Women in this group who had more than



**Figure 2.** Clinical Course and Results of Urine Cultures among Nine Women in the Placebo Group Who Had at Least One Episode of Pyelonephritis and Six Women in the Antimicrobial-Therapy Group Who Had at Least One Episode of Pyelonephritis. Results of urine cultures are shown as positive (+) or negative (-). Episodes of pyelonephritis (P) and cystitis (C) are shown. Black bars denote antimicrobial therapy.

one symptomatic episode were more likely to be sexually active (6 of 14 vs. 5 of 36,  $P=0.03$ ) and to have received a diagnosis of diabetic neuropathy (6 of 8 vs. 5 of 36,  $P=0.03$ ). No other variables were associated with an increased risk of symptomatic episodes (including prior genitourinary surgery; aboriginal ethnic origin; type 2 diabetes or a longer duration of diabetes; presence of retinopathy or nephropathy; higher blood glucose level at enrollment; and the presence of pyuria, glycosuria, or proteinuria). No variables were associated with a significant risk of symptomatic infection in the antimicrobial-therapy group. When all study subjects were considered together, independent risk factors for symptomatic urinary tract infection in-

cluded previous urinary tract infection (odds ratio, 8.6; 95 percent confidence interval, 1.7 to 41.4) and glycosuria (odds ratio, 5.1; 95 percent confidence interval, 1.03 to 25.3).

Four of 50 women in the placebo group (8 percent) and 17 of 55 in the antimicrobial-therapy group (31 percent) received at least one course of prophylactic or suppressive therapy. Among women in the placebo group, prophylaxis decreased the number of symptomatic episodes from 8.44 to 0.44 per 1000 days of follow-up. Women in the antimicrobial-therapy group received prophylactic antimicrobial agents for both symptomatic and asymptomatic recurrences, and prophylaxis was associated with a decrease in the number

of symptomatic episodes from 1.49 to 0.21 per 1000 days of follow-up. Overall, prophylaxis reduced the odds of symptomatic episodes to 0.16 (95 percent confidence interval, 0.04 to 0.59).

### DISCUSSION

We did not identify any benefits of continued screening for and treatment of asymptomatic bacteriuria in women with diabetes. Antimicrobial therapy cleared bacteriuria in the short term, but did not decrease the numbers of symptomatic episodes and hospitalizations during long-term follow-up, and the high rate of recurrent bacteriuria led to markedly increased use of antimicrobial agents. This lack of benefit is consistent with findings in other selected populations, including schoolgirls,<sup>18</sup> patients with spinal cord injuries,<sup>19</sup> and elderly institutionalized men<sup>20</sup> or women.<sup>16,21</sup> In pregnant women, however, the identification and treatment of asymptomatic bacteriuria do prevent pyelonephritis.<sup>17</sup> There is also likely to be a benefit associated with the treatment of asymptomatic bacteriuria in the first six months after renal transplantation.<sup>22</sup>

Acute pyelonephritis was relatively infrequent in both study groups. Although the difference in the rates between the two groups was not significant, the small number of events and wide confidence intervals mean a potential benefit of therapy could have been missed. The frequency of all symptomatic episodes and of hospitalizations for pyelonephritis was, however, similar in the two groups. Had there been a difference in the rates of pyelonephritis between the groups, the most likely explanation would be that persistent untreated bacteriuria increases the risk of pyelonephritis. However, few women in the placebo group had persistent bacteriuria from the time of enrollment to the occurrence of pyelonephritis. Antimicrobial therapy that eradicated or suppressed the initial episode of bacteriuria was usually given because of cystitis or other infections. Thus, although the possibility of a difference in the rates of pyelonephritis cannot be excluded, given the low rate of events, persistent bacteriuria was uncommon before the development of pyelonephritis among women in the placebo group.

Over 80 percent of the symptomatic episodes occurred in a small proportion of the study subjects. A history of urinary tract infection and being sexually active were associated with an increased risk of symptomatic episodes among women in the placebo group. Geerlings et al.<sup>23</sup> reported that symptomatic urinary tract infection was associated with sexual intercourse in women with type 1 diabetes and with asymptomatic bacteriuria in those with type 2 diabetes. As is true among nondiabetic women, a small proportion of women have frequent recurrent infections, and sexual activity and prior infection are associated with an increased risk of recurrent symptomatic episodes.<sup>24,25</sup>

The incidence of symptomatic infection among diabetic women who were receiving prophylaxis (0.2 to 0.4 per 1000 patient-days) is also comparable to that among young women without diabetes.<sup>14</sup> Thus, in our study, the risk of recurrent symptomatic urinary tract infection and the efficacy of management were consistent with those reported for women without diabetes.

The women who participated in this study were an unselected population that included both premenopausal and postmenopausal women and women with type 1 diabetes and those with type 2 diabetes, and there was a wide variation in the duration of diabetes and frequency of diabetic complications. The heterogeneity of the subjects may have limited our ability to identify a subgroup who could benefit from the treatment of asymptomatic bacteriuria. Analysis of risk factors identified neuropathy and glycosuria as diabetes-specific variables that were potentially associated with symptomatic infection. In addition, women with a serum creatinine level of more than 2.25 mg per deciliter were excluded. Further studies of the management of bacteriuria may be warranted in persons with neuropathy, glycosuria, or renal failure.

Metabolic variables were not systematically monitored, but they were similar in the two groups at the end of the study. Other investigators have also found no association between bacteriuria and indicators of metabolic control, such as the blood glucose level and the glycosylated hemoglobin value.<sup>1,9</sup> Geerlings et al.<sup>26</sup> reported that the rate of progression to microvascular or macrovascular complications and microalbuminuria was similar among diabetic women with bacteriuria and among diabetic women without bacteriuria during 18 months of follow-up. These observations all suggest that bacteriuria does not impair the control of diabetes or accelerate the rate of development of diabetic complications.

Increasing antimicrobial resistance among bacteria is a major concern. The most important variable promoting resistance is the use of antimicrobial agents. Rational use of these agents requires the identification of clinical situations in which antimicrobial therapy is not indicated. Our findings suggest that screening for and treatment of asymptomatic bacteriuria do not improve outcomes among women with diabetes. Resources invested in care for patients with diabetes should be directed to strategies shown to improve outcomes in this large and expanding population. Antimicrobial management of urinary tract infection in diabetic women should focus on the prompt identification and effective treatment of symptomatic episodes.

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## APPENDIX

The other members of the Manitoba Diabetes Urinary Tract Infection Study Group are as follows: *Laboratory support* — J. Brunka, J. Kennedy, L. Palatnick, and B. Urias; *Study coordinators* — H. Duckworth, M. Rubin, and M. Thompson; *Endocrinologists* — E. Cowden, S. Ludwig, A. Mehta, L. Murphy, G. Nyomba, S. Rowe, B. Salamon, and V. Woo; and *Infectious disease specialist* — M. Al-Hedaithy.

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