

## Treatment of uncomplicated urinary tract infection in non-pregnant women

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### Summary

A study of placebo treatment of acute symptomatic urinary tract infection in non-pregnant women showed that about 80% obtained sterile urine spontaneously within 5 months. About one-half of these had recurrent infection within a year.

Antimicrobials produced a high immediate cure rate, but only 45% maintained sterile urine for 2 years. The recurrence rate was highest during the first 2 months after treatment, and thereafter nearly constant during the subsequent 20 months. Twenty-nine percent of recurrences were recrudescences and 71% reinfections. About one-sixth of the patients had a very high recurrence rate, 2.6 infections/year, as compared with 0.32/year in the remainder. Nearly all of these patients had their first recurrence within 5 months of the initial treatment. The probability of recurrence increased with the number of previous infections. Some patients, however, after a period with many recurrences, showed a remarkable decrease in recurrence rate.

If the aim of treatment is to keep periods of bacteriuria to a minimum, it is necessary to do frequent urine cultures for at least 6 months after elimination of bacteriuria.

### Introduction

The reasons why some, but not all, apparently healthy women acquire urinary tract infection are still not known, and causal treatment is not possible. In order to relieve discomfort, prevent septicaemia and, if possible, progressive renal damage in bacteriuric patients, efforts are directed towards sterilization of the urinary tract. Innumerable studies have shown that this can be done by appropriate use of antimicrobial therapy. But it is difficult to evaluate whether treatment significantly alters the course of urinary tract infection in women.

In the present study a follow-up was made on non-pregnant women with uncomplicated urinary tract infection, in order to get an impression of the outcome of short-term therapy and the possibilities of reducing periods with bacteriuria.

### Patients and methods

During the period October 1966 to July 1968, general practitioners in the Roskilde region were

requested to refer to the medical out-patient clinic all non-pregnant women between 16 and 65 years old with symptoms of urinary tract infection. Four hundred and seventy-two women were referred. Among these, 219 women with bacteriuria and serum-creatinine values below 1.4 mg/100 ml were found. Urography performed on 210 of the bacteriuric patients revealed renal calculi in five cases, which were excluded from the study. No case of severe hydronephrosis or hydroureter was found.

The minimum criterion of bacteriuria was: more than  $10^5$  bacteria/ml in at least two consecutive mid-stream specimens, the same organism being cultured from both. In 499 out of 558 instances of bacteriuria detected during the study the diagnosis was established by culture of more than  $10^4$  organisms/ml in at least one of the specimens, by more than  $10^5$ /ml in three or more consecutive specimens, or by culture from urine aspirated by suprapubic bladder puncture. Quantitative culture of urine was made on lactose-agar and on blood-agar plates with a calibrated loop, streaking the inoculum over the whole plate with a sterile glass rod. The bacteria isolated were identified by the Department of Diagnostic Bacteriology, State Serum Institute, Copenhagen. All strains of *Escherichia coli* were typed for O- and H-antigens by the International Escherichia Centre, State Serum Institute.

Maximum urinary concentrating ability was measured by determination of urine osmolality 14-18 hr after the administration of 5 IU of vasopressin tannate in oil ('Pitressin' tannate; Parke, Davis) (DeWardener, 1956; Mabeck, 1970). Coli-antibody titre in serum was determined using the indirect haemagglutination technique (Mabeck, 1970).

In a double-blind trial, one-third of the patients were allocated to each of three therapeutic groups as shown in Table 1. Seven patients who were staff members, and seven who had severe acute pyelonephritis were excluded from the placebo trial and received treatment as scheduled for recurrent infections (see below). Nine did not complete treatment and thirty-two (including three excluded from the placebo trial) did not complete a 1-year follow-up (Table 2).

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TABLE 1. Treatment schedule

Therapeutic group	Treatment		First infection (no. of patients)	Recurrences (no. of patients)
	First to second week	Third to fourth week		
I	Antimicrobial	Chloramphenicol	68	206
II	Antimicrobial	Placebo	60	200
III	Placebo	Placebo	63	0

TABLE 2. Clinical findings

	Followed > 1 year			Followed < 1 year	Excluded from placebo trial	Total
	Group I	II	III			
Total no. of patients	57	52	53	38	14	214
Age:						
16-35 years	31	34	22	28	8	123
36-65 years	26	18	31	10	6	91
Fever and flank pain:						
Present	6	6	9	8	8	37
Absent	51	46	44	30	6	177
Radiological signs of chronic pyelonephritis:						
Present	8	6	3	5	4	26
Absent	49	44	50	25	10	178
Unknown	0	2	0	8	0	10
Serum creatinine						
1.0-1.3 mg/100 ml	18	13	20	6	4	61
< 1.0 mg/100 ml	39	39	33	28	10	149
Unknown	0	0	0	4	0	4

Tablets for the first 2 weeks' treatment were distributed in code-numbered bottles; antimicrobial agents were chosen in accordance with the result of the susceptibility test, but one-third of the bottles contained placebo tablets (Table 1). The dosages were: sulphamethizol 2 g, ampicillin 1 g, oxytetracycline 1 g, or chloramphenicol 1 g daily, divided in four doses.

In a further double-blind trial all recurrences were allocated to treatment schemes I and II (Table 1).

After initiation of treatment, urine cultures were made after 1, 2, 4 and 8 weeks, and thereafter every third month. During the follow-up all patients were instructed to report immediately upon symptoms of urinary tract infection. It was intended to follow all patients for at least 2 years, though not beyond March 1970.

#### Definitions

*Failure* is defined as persistence of bacteriuria during treatment, and *recurrence* as reappearance of bacteriuria after a period with less than  $10^4$  organisms/ml mid-stream urine. *Recrudescence* is recurrence with bacteria of the same species and serotype as found before treatment, while *reinfection* is defined as change in the urinary flora or recurrence with a different organism.

## Results

### Placebo treatment

Sixty-three patients received placebo (group III) and fifty-three of these were followed for more than 12 months (Table 2). During the first 12 months eight of these patients, because of persistent or recurrent subjective symptoms received active treatment before the urine became sterile (Fig. 1). Of the remaining forty-five patients, two had persistent bacteriuria, while forty-three attained sterile urine without further treatment. In thirty-two patients the urine became sterile within a month and in all forty-three cases within 5 months.

Recrudescence occurred in ten cases and ten patients were reinfected within a year (Fig. 1).

Relief of clinical symptoms does not indicate success of treatment. In twenty-one out of twenty-three patients with bacteriuria for more than 4 weeks the symptoms disappeared before the infection was eliminated.

### Comparison of 2 and 4 weeks' treatment

Two hundred cases of urinary tract infection were followed for 5 months or more after 2 weeks' antimicrobial treatment (group II). Two hundred and six cases, after 2 weeks' antimicrobial treatment,

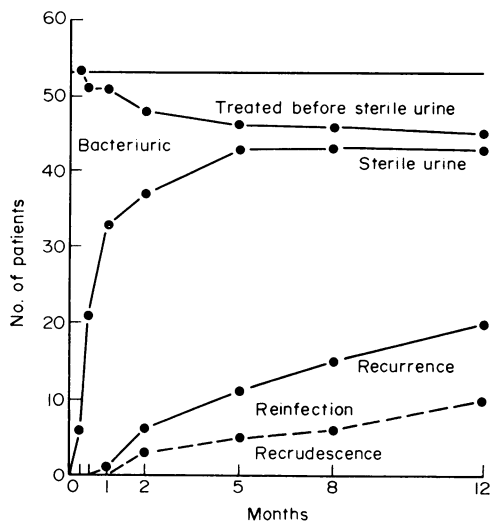


FIG. 1. Follow-up of fifty-three placebo-treated women with uncomplicated urinary tract infection.

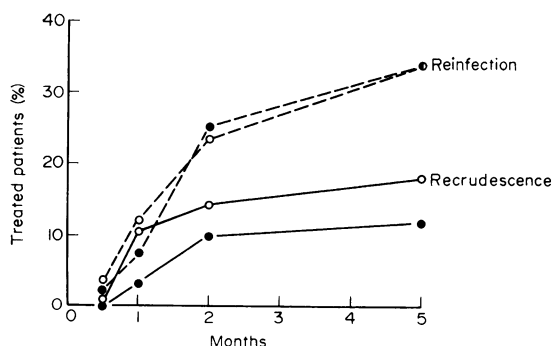


FIG. 2. Reinfection and recrudescence during 5 months' follow-up after 2 weeks' treatment with antimicrobial (o) (200 cases) and after 2 weeks' antimicrobial + 2 weeks' treatment with chloramphenicol (●) (206 cases).

received chloramphenicol for a further 2-week period (group I). In both groups the frequency of reinfection was 34% (Fig. 2), while failure or recrudescence within 5 months occurred in twenty-four cases in group I and in thirty-nine cases in group II ( $P < 0.05$ ). There are several possible explanations for this difference, but it seems too small to be of clinical importance.

**Course after treatment**

One hundred and forty-one out of 143 patients treated with sulphonamide or an antibiotic, achieved sterile urine during treatment and ninety-eight of these were followed for more than 23 months. During this follow-up recrudescence was detected in

sixteen cases and in eight of these it occurred within 2 months (Fig. 3). Reinfection was detected in forty cases.

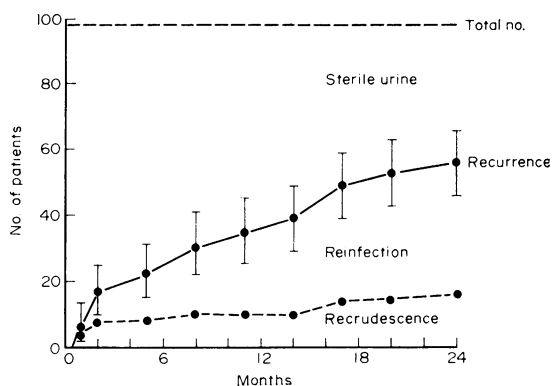


FIG. 3. Reinfection and recrudescence during 2 years' follow-up of ninety-eight women with uncomplicated urinary tract infection who attained sterile urine during treatment (95% confidence limits are shown).

Recurrence rate for a given length of time ( $t_2-t_1$ ) can be calculated in relation to patients at risk at  $t_1$ , i.e. the number of patients with sterile urine at the start of follow-up.

$$\frac{(\text{No. of recurrences during } t_2-t_1) \times 100}{(\text{Patients at risk at } t_1) (t_2-t_1)}$$

The recurrence rate was calculated for each of the first 2 months and for every 3-month observation period thereafter. Figure 4 shows that the recurrence rate was high during the first 2 months and thereafter fairly constant.

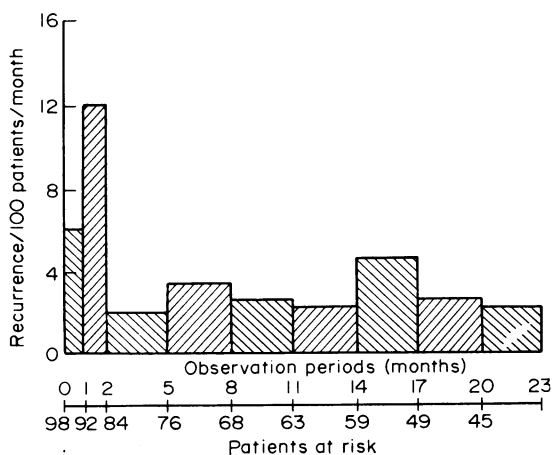


FIG. 4. Recurrence/months in % of patients with sterile urine after treatment during 2 years' follow-up of ninety-eight women with uncomplicated urinary tract infection.

The risk of further recurrences diminished with the length of time elapsing between the first and second infection. Sixty-nine actively treated patients had recurrent infection and were followed for at least 5 months after treatment of the second infection (Fig. 5). Out of twenty-nine patients who had their first recurrence within 5 months after the initial treatment, only 48% maintained sterile urine for 5 months after the second treatment. In contrast, out of forty patients who had their first recurrence more than 5 months after the initial treatment, 80% maintained sterile urine for 5 months or more after the second treatment ( $P < 0.02$ ).

The likelihood of recurrent infection within 5 months after treatment increased with the number of recurrences. After each recurrence the proportion of patients who maintained sterile urine for 5 months or more diminished by about 22% (Fig. 6). The higher recurrence rate was mainly due to an increasing number of recurrences within the first 2 months after treatment (Fig. 7).

With increasing number of recurrences the relation between failure, recrudescence and reinfection remained unchanged (Table 3), and the frequency of therapeutic failures rose only from about 1% to 8.6%. These findings suggest that in younger women with uncomplicated urinary tract infection the therapeutic problem lies not so much in eliminating bacteriuria as in detecting recurrence.

This implies the necessity of frequent urine culture in patients with a high recurrence rate. In the present study thirty-seven patients had four or more infections during the follow-up. They were followed for from 16 to 41 months (average 30.5 months) and attended the clinic an average of 17.4 times a year.

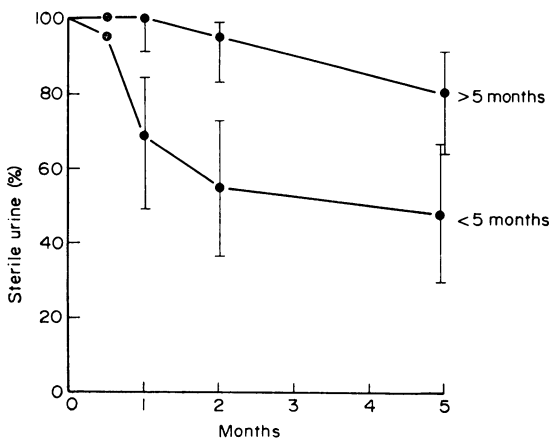


FIG. 5. Follow-up after treatment of the first recurrence which in thirty-five patients occurred within 5 months and in forty patients after more than 5 months after the initial infection (95% confidence limits are shown).

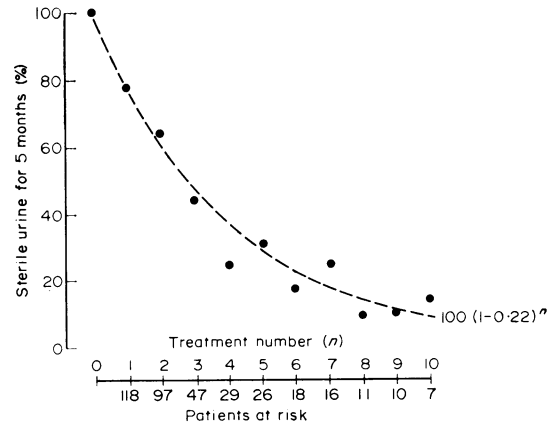


FIG. 6. The observed percentage of patients with sterile urine for 5 months after treatment of increasing number of recurrences. The broken line indicates a theoretical reduction in the proportion of patients with sterile urine as 22% after each recurrence.

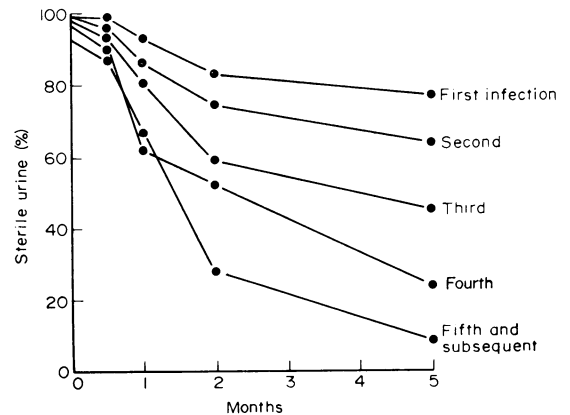


FIG. 7. Course after treatment of increasing number of recurrences.

In this group, 244 recurrences were detected, i.e. 2.6/patient-year, while the remaining patients had only 0.32 recurrences/year.

Out of these thirty-seven patients, thirteen were primarily placebo-treated and only five of these cleared up spontaneously. Patients with a high recurrence rate constituted the majority of those who had recurrent infection within 5 months after the initial treatment. Out of the twenty-four actively treated, twenty (83%) had recurrent infection within 5 months. Of the remaining patients only 14% had a recurrence within 5 months ( $P < 0.001$ ).

In most of these thirty-seven patients the recurrence rate remained unchanged during the observation period, but some cases showed a remarkable reduction in the proneness to recurrent infection

TABLE 3. Relation between failure, recrudescence, and reinfection in recurrent urinary tract infections

Infection no.	Total no. of infections	No. of recurrences during 5 months' observation	Failure (%)	Recrudescence (%)	Reinfection (%)
First	118	27	4	37	59
Second	96	33	3	24	73
Third	47	26	4	31	65
Fourth	29	22	5	31	64
Fifth and subsequent	116	105	10	27	64

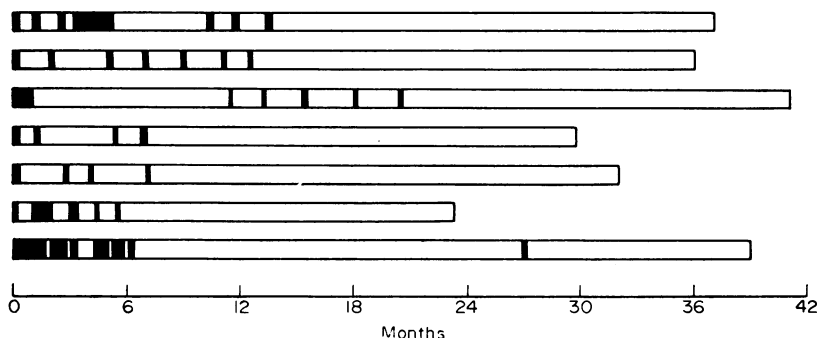


FIG. 8. Patients who after a period with a high recurrence rate maintained sterile urine for longer periods. Each black line or area indicates bacteriuria.

(Fig. 8). Whether this was a result of therapy or inherent in the natural course of the disease is not known.

The probability of reinfection increased with age ( $P < 0.05$ ), and a high recurrence rate was more frequent among patients with raised coli antibody titre ( $P < 0.05$ ) or radiological signs of chronic pyelonephritis ( $P < 0.01$ ) (Table 4). Otherwise no significant correlation was found between clinical parameters and recurrence rate.

### Discussion

The association between urinary tract infection and acute pyelonephritis is well established. A major problem is to what extent uncomplicated urinary tract infection in younger women entails a risk of developing chronic pyelonephritis and renal failure.

The possibility that urinary infection sets up a chain reaction that leads to progressive pyelonephritis without subsequent evidence of infection (Angell, Relman & Robbins, 1968; Aoki *et al.*, 1969) cannot be excluded. However, studies of children (Smellie & Normand, 1968), paraplegics (Saito, 1964), and pregnant women with bacteriuria (Kass, 1970) support the view that chronic and recurrent infection increases the risk of progressive renal damage.

Until more is known about the ultimate prognosis the aim of treatment must be to maintain sterile urine

for as long as possible. This implies the necessity of early detection of recurrences. It is, therefore, of practical importance to know for how long after eradication of infection the patients must be followed in order to reveal recurrent urinary infection.

As in other studies it was found that by appropriate treatment of uncomplicated urinary tract infection sterile urine is obtained in nearly all cases. In evaluation of the immediate response to treatment two important facts should be noted. First, relief of symptoms is no indication that therapy has been effective. Nearly all placebo-treated patients in this study showed 'clinical improvement' despite persistence of bacteriuria. Second, that 'sterile urine' means that the number of bacteria/ml does not exceed the number of organisms with which mid-stream specimens are usually contaminated. This does not exclude the possibility of bacteriuria, because, during therapy, the bacterial count may be reduced to a few hundred or thousand.

Recrudescence occurred in about 15% of the patients. In some cases this is probably due to failure to eradicate the organisms from the urinary tract. But if the bowel flora remains unchanged it is possible that a large proportion of reinfection within the first months after treatment are caused by the same organism that was responsible for the initial infection. Therefore, recrudescence represent the maximum number of cases in which the urinary tract

TABLE 4. Recurrences in relation to clinical findings on admission

	Sterile urine for 1 year	Few recurrences ( $<4$ )	Many recurrences ( $>4$ )	Total
Total no. of patients	69 (57%)	27 (23%)	24 (20%)	120
Age:				
16-35 years	66%*	18%	16%	72
36-65 years	46%	29%	25%	48
Fever and flank pain:				
Present	44%	39%	17%	18
Absent	59%	20%	21%	102
ESR:				
$> 20$ mm/hr	55%	30%	15%	40
$< 20$ mm/hr	59%	19%	22%	80
Maximum urinary concentrating ability:				
$< 800$ mOsm/kg	53%	25%	22%	55
$> 800$ mOsm/kg	63%	16%	21%	38
Unknown				27
Urographic signs of chronic pyelonephritis:				
Present	41%	12%	47%†	17
Absent	60%	24%	16%	101
Unknown				2
Reciprocal coli antibody titre:				
Raised ( $> 1280$ )	24%	35%	41%*	17
Normal ( $< 1280$ )	60%	24%	16%	45
Unknown				58
Infecting organism:				
<i>E. coli</i>	59%	21%	19%	98
Coag-neg. Staphylococci	67%	20%	13%	15
Other organisms				7

Placebo-treated patients and patients followed for less than 1 year are excluded.

\*  $P < 0.05$ .

†  $P < 0.01$ .

has not been sterilized, but does not rule out the possibility of reinfection.

Uncomplicated urinary tract infection in women shows a tendency towards spontaneous remission. Kass, Savage & Santamarina (1965) found, on re-examination of women with asymptomatic bacteriuria detected in population surveys, that 'each year, in about one-fourth of the adult female population the infection clears spontaneously'. Asscher *et al.* (1969), in a 1-year follow-up of forty-five women with asymptomatic bacteriuria, who had been given a placebo, found that 36% had sterile urine. Similar results have been reported by Freedman, Seki & Phair (1965). The remission rates found in these studies are probably too low because some patients, after their infection had cleared up spontaneously, may have become reinfected within the observation period.

In the present study about 80% of placebo-treated patients attained sterile urine spontaneously. But nearly one-half of them had recurrent infection within the first year. Recurrences were treated and

the proportion of patients with sterile urine after 1 year is, therefore, not comparable with previous studies. However, 43% maintained sterile urine after spontaneous remission, and the possibility that acute symptomatic infections clear up more readily than asymptomatic infections cannot be ruled out. The difference between the course of acute symptomatic infections and asymptomatic infections revealed by screening programmes might be due to an over-representation of chronic and long-standing bacteriuria in screening studies.

In comparison with placebo treatment, antimicrobials produced a high immediate cure rate but only 60% maintained sterile urine for 1 year. In other studies even smaller differences between treated and untreated have been found (Asscher *et al.*, 1969; Freedman *et al.*, 1965).

Most recurrences in uncomplicated urinary tract infections are due to reinfection. In the present study, 71% of recurrences were reinfections. Similar findings have been reported by Kunin (1970) and McGeachie (1966), while in complicated urinary

tract infection and in advanced chronic pyelonephritis the majority of recurrences are due to recrudescence (Turck, Anderson & Petersdorf, 1966; McCabe & Jackson, 1965).

Recrudescence due to insufficient sterilization of the urinary tract will result in recurrence shortly after discontinuation of therapy. This contributes to the high recurrence rate during the first 2 months after treatment. Thereafter, in the present study, the recurrence rate became constant for the next 20 months. This seems to be in contrast with the course in complicated urinary tract infection or advanced chronic pyelonephritis. In such patients McCabe & Jackson (1965) found that the reinfection rate decreased from 3.2%/month during the first year to 0.5% during the second, and 0.2% during the third year after elimination of bacteriuria. In their study reinfection accounted for one-third of recurrences only.

Patients with many recurrences probably constitute a group with an increased risk of developing renal failure and they should receive special attention. In the present study one-sixth of the patients accounted for 70% of all recurrences detected. The frequency of spontaneous remission was lower in this group, while the proportion of recurrences due to failures or recrudescence did not increase with the number of infections.

The majority of patients with many recurrences had their first recurrence within 5 months after the initial treatment. As no single symptom or sign can predict which patient will have recurrent infection, it is necessary to follow patients with uncomplicated urinary tract infection for at least half a year after treatment in order to identify those who have recrudescence or a high recurrence rate.

Follow-up means culture of urine at regular intervals, because 39% of recurrences were asymptomatic and many cases had only transient clinical symptoms.

*Figures 1, 3, 4 and 6 are taken from Postgraduate Medical Journal (Sept. Suppl.) 47, 31.*

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