

# Primary care

## Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial

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### Abstract

**Objective** To assess the effectiveness of antibiotic treatment of women with symptoms of urinary tract infection but negative urine dipstick testing.

**Design** Prospective, double blind, randomised, placebo controlled trial.

**Setting** Primary care, among a randomly selected group of general practitioners in Christchurch, New Zealand.

**Participants** 59 women aged 16-50 years presenting with a history of dysuria and frequency in whom a dipstick test of midstream urine was negative for both nitrites and leucocytes. Participants with complicated urinary tract infection were excluded.

**Intervention** Trimethoprim 300 mg daily for three days or placebo.

**Main outcome measures** Self reported diary of symptoms for seven days, recording the presence or absence of individual symptoms each day, followed by a structured telephone questionnaire after seven days. The main clinical outcome was resolution of dysuria at three and seven days and median time to resolution. Secondary outcomes were resolution of other symptoms.

**Results** The median time for resolution of dysuria was three days for trimethoprim compared with five days for placebo ( $P=0.002$ ). At day 3, five (24%) of patients in the treatment group had ongoing dysuria compared with 20 (74%) in the placebo group ( $P=0.005$ ). This difference persisted until day 7: two patients (10%) in the treatment group *v* 11 (41%) in the placebo group;  $P=0.02$ . The number needed to treat was 4. The median duration of constitutional symptoms (feverishness, shivers) was reduced by four days.

**Conclusions** Although a negative dipstick test for leucocytes and nitrites accurately predicted absence of infection when standard microbiological definitions were used (negative predictive value 92%), it did not predict response to antibiotic treatment. Three days' treatment with trimethoprim significantly reduced dysuria in women whose urine dipstick test was negative. These results support the practice of empirical antibiotic use guided by symptoms. Balancing the competing interests of symptom relief and the minimisation of antibiotic use remains a dilemma—further research is needed to determine clinical predictors of response to antibiotics.

### Introduction

Infections of the urinary tract are extremely common, and the numbers of patients presenting to general practice with this condition represent considerable morbidity and workload.<sup>1</sup> Because the symptoms of dysuria and frequency are unpleasant, doctors are under pressure from patients to provide relief.<sup>2 3</sup> However, not all such symptoms are associated with growth of bacteria in a standard midstream urine specimen. More detailed microbiological investigation of women with apparently negative urine cultures on standard testing indicate that a proportion of them have low count bacteriuria.<sup>4</sup> Urine testing with dipsticks that detect the presence of leucocytes and nitrites is commonly used in primary care to predict the subsequent diagnosis of urinary tract infection as determined by standard midstream urine culture and to guide the use of antibiotics. In one general practice study, the presence of leucocytes or nitrites in turbid urine had a positive predictive value of finding a pure growth on subsequent culture of around 66%.<sup>3</sup> Conversely, a negative dipstick test for both leucocytes and nitrites has a negative predictive value of finding a pure growth on subsequent culture of 80-98.5%.<sup>2 3</sup> In 2000 we carried out an epidemiological study to determine the prevalence of antibiotic resistance in bacteria causing uncomplicated urinary tract infections in the community and confirm the negative predictive value of the dipstick.<sup>5</sup>

Of 374 specimens collected, 96 (26%) were negative for both leucocytes and nitrites.<sup>5</sup> Eight of these (8%) contained pure growth cultures above the standard conservative cut-off point of  $100 \times 10^6$  colony forming units per litre.<sup>6</sup> The negative predictive value of the dipstick test was 92%.

The approach to women with symptoms of uncomplicated urinary tract infection and positive urine dipstick results is to give empirical antibiotic treatment.<sup>7-9</sup> Recommendations for the treatment of women with symptoms and negative dipstick results vary. Some suggest empirical treatment,<sup>1 10</sup> but others do not.<sup>7 8 11</sup> We carried out a pragmatic trial of antibiotic compared with placebo in women with symptoms of uncomplicated urinary tract infection and negative dipstick results.

### Methods

We designed the study as a double blind randomised placebo controlled trial. The intervention was treatment with trimethoprim 300 mg daily for three days.



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### Participants

We invited women to participate who were aged between 16 and 50 and presenting with a history of dysuria and frequency to general practitioners from the randomly selected Christchurch sentinel network.<sup>5</sup> Seventy five (91%) of the original 82 randomly selected general practitioners in the network were participating in a surveillance study, and 30 (40%) of these agreed to recruit patients for the randomised controlled trial. Exclusion criteria were a dipstick test that was positive for leucocytes or nitrites, complicated urinary tract infections, pregnancy, or known allergy to trimethoprim. We also excluded women with proved urinary tract infection or treatment for presumed urinary tract infection in the past month.

All the women who agreed to participate provided a midstream urine specimen that their general practitioner tested immediately with a standard urine dipstick and then sent for microbiological examination and culture. We randomly allocated patients whose dipstick test was negative for both leucocytes and nitrites to receive either three days of trimethoprim 300 mg (standard treatment) or placebo. To randomise the participants, the biostatistician chose SAS code, which used random block lengths with a maximum of 10 to generate a random sequence for the medication packs. This went to a dispensing pharmacist, together with a sequential alphanumeric code list. The pharmacist prepared identical placebo and active drug capsules and attached an alphanumeric code to the medication bottles that the patients received from their general practitioner. The pharmacist put the codes with the list identifying allocation to placebo or treatment in a sealed envelope. The study team and general practitioners enrolling patients had no access to the code list until the data collection was complete. Labels preprinted with the code were provided to attach to the patient's clinical notes as well as the initial urinary specimen form and questionnaire. General practitioners, investigators, and research nurses were all blind to allocation until the data collection was complete.

### Data collection

Two accredited pathology laboratories (International Accreditation New Zealand) used standard techniques to test the urine specimens. A 0.001 ml loop was used to plate the specimens on to MacConkey agar and sheep blood agar. Plates were incubated at 37°C for 48 hours and colony counts recorded. We defined pyuria as 20 leucocytes or more per ml of urine on microscopy and clinically relevant bacteriuria as  $\geq 10^5$  organisms/ml of urine.

Participants completed a short written questionnaire at the surgery. This asked about demographic details, current symptoms, including, on the day the participant entered the trial, the presence or absence of dysuria, increased urinary frequency, low back pain, abdominal pain, appearance of blood in the urine, itching, and feeling "hot or shivery." Women were also asked about potential risk factors for infection, including use and type of contraceptive, recent sexual activity, past history of infection, and use of other preparations to alleviate symptoms. Participants received a seven day diary to record their symptoms and return by mail. They recorded the presence or absence of individual symptoms each day. We contacted all women after seven days and administered a structured telephone questionnaire, recording the presence or absence of each symptom. Where a symptom was absent and had been recorded as present on the day 1 questionnaire, we asked the woman to recall the day on which the symptom resolved. Adverse effects potentially related to medica-

tion and any other treatments taken were recorded. We asked participants to provide a second midstream urine specimen for microbiological examination and culture.

The main outcome was resolution of dysuria in the intervention and control groups at three and seven days, and median time to resolution. Secondary outcomes were resolution of other symptoms. We investigated predictors of response to treatment.

### Statistical methods

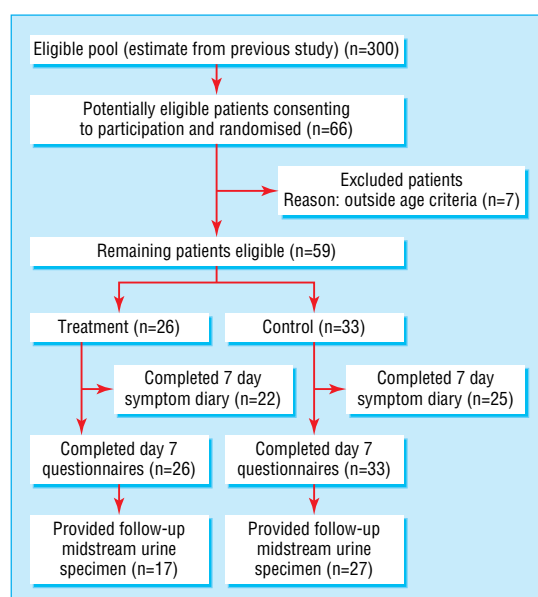
The study was powered to detect clinically important differences between the two groups. With 30 participants in each arm, using  $\alpha_2 = 0.05$ , the study has 78% power to show a difference between groups if the "true" rates are such that symptoms will not resolve in only 10% of women taking antibiotics compared with 40% of women taking placebo. This sample size has 99% power to detect a difference between groups if the true rates are such that symptoms will not resolve in only 25% of women taking antibiotics compared with 75% of women taking placebo.

We used the median test to analyse days to resolution by symptom, and, where appropriate, we also calculated the number needed to treat. We included women whose symptoms had not resolved in this analysis, with censoring after day 7. We used the  $\chi^2$  test for contingency tables to analyse proportions. We used SAS, version 8.02 (SAS Institute, Cary, North Carolina, USA), to carry out all our analyses.

### Results

The trial ran from November 2001 until November 2003. Sixty six patients who fitted the case definition for uncomplicated urinary tract infection with a negative dipstick result consented to participate in the study and were randomised. We decided that collecting accurate screening log data from a large group of general practitioners about every woman presenting with symptoms of urinary tract infection over an extended period was impractical. Using data from our 2000 study among the same group of general practitioners,<sup>5</sup> we estimated that the number of dipstick negative patients in the eligible age range seen over a two year period by these 30 general practitioners would be 300 (five dipstick negative patients per year per general practitioner). The remainder were not recruited because the general practitioner did not remember to approach them about the study or did not have time to complete the informed consent process, or the patient did not consent to involvement. This gives an estimated response rate of 20% from the potentially eligible pool. Seven patients were excluded after randomisation (three in one arm and four in the other) and did not complete the study as they were outside the inclusion criteria for age. This left 26 patients in the treatment arm and 33 in the placebo arm (numbers are unbalanced as each general practice had some unused packs). Figure 1 shows the flow of participants through the trial. For the 12 participants who did not complete the symptom diary, we used the data from the telephone call on day 7. In this way we ensured that for all participants, complete data were available on the day when their symptom resolved.

The treatment and placebo groups were similar in demographic characteristics (table 1). Among all women who reported dysuria on day 1, the median time for resolution of dysuria was three days in the trimethoprim group and five days in the placebo group ( $P = 0.002$ ; table 2). At day 3, 24% of patients in the treatment group who had dysuria on day 1, still had dysuria compared with 74% of the placebo group ( $P = 0.005$ ; table 3). This difference was still present at day 7; only



**Fig 1** Flow of participants through the trial

**Table 1** Patients' characteristics at baseline. Values are numbers (percentages) of patients unless otherwise indicated

Characteristic	Placebo group (n=33)	Treatment group (n=26)
Mean (SD) age in years	36 (8.8)	35 (8.4)
Ethnicity (New Zealand European)	25 (76)	23 (88)
Previous self reported urinary tract infection	29 (88)	24 (92)
Mean (SD) No of children	1.6 (1.3)	1.3 (1.3)

**Table 2** Days to resolution by symptom

Symptom*	No (%) of women with symptom at baseline		Median No of days to resolution†		P value for difference	Number needed to treat (95% CI)
	Placebo (n=33)	Treatment (n=26)	Placebo (n=33)	Treatment (n=26)		
Dysuria (48 women)	27 (82)	21 (81)	5	3	0.002	4 (1.9 to 14.1)
Frequency (55 women)	30 (91)	25 (96)	5	5	0.97	—
Appearance of blood in urine (8 women)	4 (12)	4 (15)	—‡	—‡	—‡	—
Itching (22 women)	10 (30)	12 (46)	7.5	5	0.38	—
Abdominal pain (47 women)	26 (79)	21 (81)	6	5.5	1.00	—
Feverishness and shivers (22 women)	11 (33)	11 (42)	6	2	0.02	3 (1.3 to 8.3)
Low back pain (31 women)	16 (48)	15 (58)	>6	5	0.06	—

\*Number varies as not all women experienced every symptom.

†In patients experiencing the symptom at baseline.

‡Numbers too small for comparison.

**Table 3** Patients with symptom at baseline still experiencing symptom after day 3 and day 7

Symptom	No of patients taking placebo (treatment)	Patients with symptom after day 3*					Patients with symptom after day 7*				
		Placebo		Treatment		P value for difference‡	Placebo		Treatment		P value for difference‡
		No	% (95% CI)†	No	% (95% CI)†		No	% (95% CI)†	No	% (95% CI)†	
Dysuria	27 (21)	20	74 (54 to 89)	5	24 (8 to 47)	0.0005	11	41 (22 to 61)	2	10 (1 to 30)	0.02
Frequency	30 (25)	22	73 (54 to 88)	13	52 (31 to 72)	0.10	13	43 (25 to 63)	10	40 (21 to 61)	0.80
Appearance of blood in urine	4 (4)	2	50 (7 to 93)	0	—	0.43	1	25 (1 to 81)	0	—	1.00
Itch	10 (12)	8	80 (44 to 97)	6	50 (21 to 79)	0.20	5	50 (19 to 81)	4	33 (10 to 65)	0.67
Abdominal pain	26 (21)	17	65 (44 to 83)	12	57 (34 to 78)	0.56	12	46 (27 to 67)	8	38 (18 to 62)	0.58
Feverishness or shivers	11 (11)	5	46 (17 to 77)	0	—	0.04	4	36 (11 to 69)	0	—	0.09
Low back pain	16 (15)	11	69 (41 to 89)	8	53 (27 to 79)	0.38	8	50 (25 to 75)	4	27 (8 to 55)	0.18

\*Of patients experiencing the symptom at baseline

†Exact 95% confidence intervals for percentage.

‡ $\chi^2$  test or Fisher's exact test as appropriate.

10% of the treatment group who reported dysuria on day 1 were experiencing dysuria, compared with 41% of the placebo group ( $P=0.02$ ). Less than a third of patients in each group experienced constitutional symptoms of feverishness or shivers. However, among those who had symptoms, the median time from clinical presentation and treatment initiation to resolution of feverishness or shivers was two days in the trimethoprim arm, compared with six days in the placebo arm ( $P=0.02$ ). At day 3, 46% of patients in the placebo group were still feeling hot and shivery compared with none of the treatment group ( $P=0.04$ ). The difference between groups did not reach significance at day 7 (0% v 36%,  $P=0.09$ ). The median time to resolution or proportion experiencing symptoms at day 3 and 7 for urinary frequency, abdominal pain, itch, or low back pain did not differ.

No patient or illness characteristic predicted response to treatment at day 3. Twenty six participants had  $\geq 20$  leucocytes per ml in their urine on microscopy, 13 in each arm, and this did not predict response to treatment. In the placebo arm, 6/13 (46%) of those who reported no dysuria at day 3 and 7/20 (35%) who still reported dysuria had pyuria at trial entry. In the treatment arm, 8/19 (42%) of those who reported no dysuria at day three and 5/7 (71%) who still reported dysuria had pyuria at trial entry. Five women had microbiological evidence of bacterial infection on midstream urine testing when we used standard criteria of  $\geq 20$  leucocytes/ml of urine and pure growth of  $\geq 10^5$  organisms/ml of a uropathogen.<sup>6</sup> Four of these grew *Escherichia coli* and one *Klebsiella pneumoniae*. Three were in the treatment arm and two in the placebo arm. The negative predictive value of the dipstick in this study was therefore 92%. Six women had low count bacteriuria, three in each arm, and this did not predict response to treatment.

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We obtained follow-up urine specimens from 42 participants (71%). Two participants had clinically significant bacteriuria (*E coli* in both cases), both of whom were in the placebo arm, and 13 had  $\geq 20$  leucocytes/ml in their urine on microscopy.

We saw few adverse effects in either arm. Six patients (18%) in the placebo arm and three (12%) in the treatment arm reported minor symptoms (nausea, sore mouth, itching skin, sedation after taking medication, mouth ulceration, and thrush). Nine patients in each group (treatment group 29%, placebo group 35%) had used other preparations. These included cranberry juice, urinary alkalinisers, herbal preparations, and homeopathic remedies.

## Discussion

Compared with placebo, administration of trimethoprim notably shortened the median duration of dysuria in women with symptoms of uncomplicated urinary tract infection in whom dipstick results were negative. For those women who reported dysuria at baseline, the duration of dysuria from the time of clinical presentation was shortened by a median of two days. Four women needed to be treated with trimethoprim to shorten the duration of symptoms for one woman (number needed to treat = 4). Similarly, the median duration of constitutional symptoms indicating infection (feverishness, shivers) was reduced by four days. The duration of any other symptoms did not differ. These results indicate a bacterial or other infectious cause for the symptoms that was missed by dipstick testing and standard testing in a diagnostic laboratory. The resolution of symptoms that generally accompany infection (feeling feverish or shivery) would provide some support for an atypical or occult infective cause, implying that these women do not have "urethral syndrome," a diagnosis of exclusion. It is known that a past history of urinary tract infection also increases the risk of subsequent infection, and 90% of the women in the sample reported a past history of similar symptoms. Although this high rate is not found in the general population of women, it is consistent with other studies of women presenting in primary care with urinary tract infections.<sup>12</sup> An alternative but less likely hypothesis is that trimethoprim has an effect other than its bactericidal one in reducing symptoms.

### Strengths and limitations of the study

The pragmatic design of this trial is its strength. Trials of antibiotics are usually limited to patients who have been screened for microbiologically confirmed infection, with the assumption that patients who do not show infection will not respond to treatment. In general practice treatment for uncomplicated urinary tract infection is usually empirical and not informed by individual microbiological results. Response to treatment is also an important indicator of clinical outcome, given that symptom relief, not microbiological cure, is the main aim of treatment. The negative predictive value of 92% for the dipstick test in this study was consistent with international studies and implies that the results are generalisable to other primary care populations.<sup>3 2</sup>

The study had some limitations. The unexpectedly high positive response to antibiotics reduced the power to assess predictors of response to treatment, as there were so few non-responders. Generalisability must be considered in the light of the fact that not all potentially eligible women were recruited for the study. Other organisms have been implicated in dysuria and frequency. We did not test for *Chlamydia trachomatis*. However, *C trachomatis* does not respond to trimethoprim and if cases were inadvertently included they would not have accounted for the observed effect of trimethoprim.

A proportion of these patients may have had low count bacteriuria with conventional pathogens reflecting cystitis, urethritis,

or "female prostatitis" and might be expected to respond to trimethoprim.<sup>4 6 13-16</sup> It is of interest that Stamm also identified a separate group of patients without pyuria who had an acute dysuria syndrome very similar to those with low count bacteriuria but for which no organism could be found.<sup>4</sup> To our knowledge this group has not been investigated further to assess the effectiveness of treatment.

### Implications for clinical practice

If the results of this study with trimethoprim are confirmed in similar studies the use of urine dipstick testing and standard midstream urine culture and microscopy to inform prescribing decisions in women with symptoms of uncomplicated urinary tract infection should be reviewed. These results show that empirical treatment with antibiotics (dipstick positive and dipstick negative) patients presenting in primary care is justified irrespective of dipstick findings. The downside of such a strategy is an increase in adverse events, superinfection, and increased antibiotic pressure with the consequent promotion of bacterial resistance. Such a policy would further highlight the tension between relieving symptoms expeditiously with the desire to minimise unnecessary antibiotic use.<sup>17</sup> More discriminating ways to avoid unnecessary antibiotic exposure are needed.

### Conclusions

Although negative dipstick results are useful in predicting which women aged 16-50 presenting with symptoms of urinary tract infection will have a negative urine culture, these results show that it does not follow that this will predict response to antibiotic treatment. Further clinical and microbiological study of the group of women who seem not to have infection yet whose symptoms are relieved more quickly with a short course of trimethoprim is needed to understand the aetiology of symptoms in this group. At a population level, a need also exists to find a more discriminating way to avoid unnecessary antibiotic exposure in all women presenting with symptoms of urinary tract infection. This requires larger epidemiological studies of women presenting with dysuria and frequency in general practice, assessing a range of clinical predictors using response to antibiotics as the primary outcome.

This study would not have been possible were it not for the (unpaid) efforts of the general practitioners and practice nurses of the sentinel network who identified and recruited suitable patients. Research nurses Toni Stewart, Felicity Beats, and Margaret Sutherland were responsible for the data collection. Alison Parsons provided invaluable office support for the network and follow-up of missing data. Rosemary Ikram from Medlab South and Ben Harris from Southern Community Laboratories in Christchurch facilitated smooth identification and processing of results from all specimens.

Contributors: DR and LT conceived and designed the study and interpreted the data. DR designed the protocol, coordinated the study, set up the database, participated in the data analysis and wrote the first draft of the paper with LT. SC advised on microbiological aspects of the design, planning, conduct, and analysis of the study and contributed to the writing of the paper. LF directed and carried out the statistical analysis, contributed to the writing of the paper, and took the lead in writing the sections on data analysis. DR is the guarantor.

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## What is already known on this subject

Antibiotics are effective in reducing symptom duration in microbiologically determined urinary tract infection

Dipstick urine testing is useful in predicting patients who are unlikely to have microbiological evidence of a urinary tract infection

It has been assumed that this group of patients will not benefit from antibiotics

No prospective randomised controlled trials have tested the effectiveness of antibiotics in reducing duration of symptoms in this group

## What this study adds

Trimethoprim reduces the duration of dysuria in women with symptoms of uncomplicated urinary tract infection and negative dipstick result by a median time of two days

The number needed to treat is four

An infectious cause for the symptoms is likely in this group of women, which is not being diagnosed by using the current approach

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