

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

Dee Richards, Les Toop, Stephen Chambers, Lynn Fletcher

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 *vs* 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

Urine testing with dipsticks that detect the presence of leucocytes and nitrites is commonly used in primary care to predict subsequent diagnosis of urinary tract infection by midstream urine culture and guide the use of antibiotics. In general practice the presence of leucocytes or nitrites in turbid urine has a positive predictive value of finding a pure growth on subsequent culture of around 66%.¹ 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%.^{1 2}

The approach to women with symptoms of uncomplicated urinary tract infection and positive urine dipstick results is to give empirical antibiotic treatment. Recommendations for the treatment of women with symptoms and negative dipstick results vary—some suggest empirical treatment, but others do not. This group is not small. In a previous epidemiological study 26% of samples were dipstick negative.³ Of these only 8% contained pure growth cultures above the standard conservative cut-off point.⁴ 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

This was a double blind randomised placebo controlled trial. The intervention was treatment with trimethoprim 300 mg daily for three days.

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

Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, PO Box 4345, Christchurch, New Zealand
Dee Richards
senior lecturer
Les Toop
professor
Lynn Fletcher
biostatistician

Department of Pathology, Christchurch School of Medicine and Health Sciences
Stephen Chambers
professor

Correspondence to: D Richards
derelie.richards@chmeds.ac.nz

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the randomly selected Christchurch sentinel network.³ 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 women 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.

Data collection

Two accredited pathology laboratories used standard techniques to test the urine specimens. 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, including demographic details and current symptoms. Women were also asked about potential risk factors for infection. Participants received a seven day diary to record their symptoms daily and return by mail. 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 medication 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

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 χ^2 test for contingency tables to analyse proportions.

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 were randomised. This gives an estimated response rate of 20% from the potentially eligible pool (see bmj.com).³ Seven patients were excluded after randomisation. This left 26 patients in the treatment arm and 33 in the placebo arm.

The treatment and placebo groups were similar in demographic characteristics. 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 (table 1). 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 (table 2). This difference still reached significance at day 7. Less than a third of patients in each group experienced constitutional symptoms of feverishness or shivers. However, among those who had these symptoms, those on trimethoprim took a shorter time to resolve. Other symptoms did not differ significantly between the groups in time to resolution or proportion experiencing symptoms at day 3 and day 7.

No patient or illness characteristic predicted response to treatment at day 3. Twenty six participants had ≥ 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 ≥ 20 leucocytes/ml of urine and pure growth of $\geq 10^5$ organisms/ml of a uropathogen. 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.

We obtained follow-up urine specimens from 42 participants (71%). Two participants had clinically significant bacteriuria (*E coli* in both cases), both

Table 1 Days to resolution of dysuria

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 2 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.

‡ χ^2 test or Fisher's exact test.

of whom were in the placebo arm, and 13 had ≥ 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. Nine patients in each group (treatment group 29%, placebo group 35%) had used other preparations, including cranberry juice, urinary alkalinisers, herbal preparations, and homeopathic remedies.

Discussion

Compared with placebo, administration of trimethoprim markedly 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. Similarly, the median duration of constitutional symptoms indicating infection was reduced by four days. 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 would provide some support for an atypical or occult infective cause, implying that these women do not have "urethral syndrome," a diagnosis of exclusion. A past history of urinary tract infection also increases the risk of subsequent infection, and 90% of the women in the sample reported a history of similar symptoms. This high rate is consistent with other studies of women presenting in primary care with urinary tract infections.⁵ 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 microbiologi-

cal 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.^{1,2}

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 including *Chlamydia trachomatis* have been implicated in dysuria and frequency. *C trachomatis* does not respond to trimethoprim and would not have accounted for the observed effect.

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.^{4,6-11} In addition Stamm et al also identified a separate group

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; it is not being diagnosed by using the current approach

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.⁶

Implications for clinical practice

If these findings are confirmed empirical treatment with antibiotics of (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. This further highlights the tension between relieving symptoms expeditiously with the desire to minimise unnecessary antibiotic use.

Conclusions

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. At a population level, we need a more discriminating way to avoid unnecessary antibiotic exposure in all women presenting with symptoms of urinary tract infection.

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One hundred years ago

The foundation of the British Museum

DOES the British public, or even the medical profession, fully realize that the nation owes that magnificent institution, the British Museum, to the liberality of a doctor? Its true begetter was Sir Hans Sloane, a fashionable physician of the eighteenth century. . . . Hans Sloane, who was of Scottish descent, was born in County Down in 1660. Even in boyhood he collected specimens, and the taste grew upon him till it became the ruling passion of his life. Natural history led him to medicine, which in those spacious days comprehended all science within itself. . . . With a rapidity that seems enviable to us whose professional lot lies in more arduous times, Sloane was elected a Fellow of the Royal Society in 1685, and was admitted to the Fellowship of the College of Physicians in 1687. In that year there came to him an offer to go to Jamaica as physician to the Duke of Albemarle, who had been appointed Governor of that island. . . . Within eighteen months the Duke died, and his physician's nominal occupation was gone. Sloane's real occupation, however, had been the gathering of materials for the museum which was his lifework. He returned to England in 1689, loaded with the spoils of his expeditions . . . and became a highly prosperous physician. The Court and the aristocracy, we are told, had the "greatest confidence in his prescriptions." Queen Anne took counsel of him; George the Second made him the keeper of the royal constitution; George the First had previously made him a baronet and appointed him Physician-General to the Army. The

University of Oxford gave him its doctor's degree in 1701, and he was President of the College of Physicians for sixteen years. He was appointed Secretary of the Royal Society in 1693, and succeeded Isaac Newton in the Presidency of that body in 1727. . . . Throughout his life Sloane went on adding to his museum, and he accumulated a vast collection, which included books, manuscripts, pictures, medals, and coins, as well as objects of natural history. He retired from practice in 1721, and died in 1753 at the age of 93 leaving in his will directions that his museum, which was valued at £50,000, should be offered to the nation for the sum of £20,000. The offer was accepted by Parliament, and the collection formed the nucleus of the British Museum, which was opened to the public in 1759. During the greater part of his professional life Sloane lived in Bloomsbury Square, close to the site of the future British Museum. Towards the end of his life he retired to Chelsea, where he had purchased a manor house and land, which is now covered by the stately mansions of the Cadogan estate. One of his daughters became the wife of the second Lord Cadogan, and the physician's own name is perpetuated in Sloane Street and Hans Place. If Sloane was wealthy, he was also liberal. He gave the Apothecaries' Society their famous Physic Garden at Chelsea; he took part in the establishment of the Foundling Hospital, and he was never deaf to any deserving appeal made in the name of charity.

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