

Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study

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GM Leydon, A Arscott and M Mullee



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P Little,^{1,*} S Turner,¹ K Rumsby,¹
G Warner,² M Moore,³ JA Lowes,⁴
H Smith,^{1,5} C Hawke,⁶ D Turner,⁷
GM Leydon,¹ A Arscott¹ and M Mullee¹

¹Community Clinical Sciences Division (CCS), University of Southampton, UK

²Nightingale Surgery, Greatwell Drive, Romsey, UK

³Three Swans Surgery, Rollestoke Street, Salisbury, UK

⁴Southampton Health Protection Agency Laboratory, Southampton, UK

⁵Brighton Medical School, Brighton, UK (present address)

⁶School of Rural Health, University of Sydney, Australia

⁷Wessex Institute, University of Southampton, UK

*Corresponding author

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 97/14/06. The contractual start date was in September 2001. The draft report began editorial review in July 2007 and was accepted for publication in October 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study

P Little,^{1*} S Turner,¹ K Rumsby,¹ G Warner,² M Moore,³ JA Lowes,⁴ H Smith,^{1,5} C Hawke,⁶ D Turner,⁷ GM Leydon,¹ A Arscott¹ and M Mullee¹

¹Community Clinical Sciences Division (CCS), University of Southampton, UK

²Nightingale Surgery, Greatwell Drive, Romsey, UK

³Three Swans Surgery, Rollestone Street, Salisbury, UK

⁴Southampton Health Protection Agency Laboratory, Southampton, UK

⁵Brighton Medical School, Brighton, UK (present address)

⁶School of Rural Health, University of Sydney, Australia

⁷Wessex Institute, University of Southampton, UK

*Corresponding author

Objectives: To estimate clinical and dipstick predictors of infection and develop and test clinical scores; to compare management using clinical and dipstick scores with commonly used alternative strategies; to estimate the cost-effectiveness of each strategy; and to understand the natural history of urinary tract infection (UTI) and women's concerns about its presentation and management.

Design: There were six studies: (1) validation development for diagnostic clinical and dipstick scores; (2) validation of the scores developed; (3) observation of the natural history of UTI; (4) randomised controlled trial (RCT) of scores developed in study 1; (5) economic analysis of the RCT; (6) qualitative study of patients in the RCT.

Setting: Primary care.

Participants: Women aged 17–70 with suspected UTI.

Interventions: Patients were randomised to five management approaches: empirical antibiotics; empirical delayed antibiotics; target antibiotics based on a higher symptom score; target antibiotics based on dipstick results; or target antibiotics based on a positive mid-stream specimen of urine (MSU).

Main outcome measures: Antibiotic use, use of MSUs, rates of reconsultation and duration, and severity of symptoms.

Results: (1) 62.5% of women had confirmed UTI. Only nitrite, leucocyte esterase and blood independently predicted diagnosis of UTI. A dipstick rule – based

on having nitrite or both leucocytes and blood – was moderately sensitive (77%) and specific (70%) [positive predictive value (PPV) 81%, negative predictive value (NPV) 65%]. A clinical rule – based on having two of urine cloudiness, offensive smell, reported moderately severe dysuria, moderately severe nocturia – was less sensitive (65%) (specificity 69%, PPV 77%, NPV 54%). (2) 66% of women had confirmed UTI. The predictive values of nitrite, leucocyte esterase and blood were confirmed. The dipstick rule was moderately sensitive (75%) but less specific (66%) (PPV 81%, NPV 57%). (3) Symptoms rated as moderately bad or worse lasted 3.25 days on average for infections sensitive to antibiotics; resistant infections lasted 56% longer, infections not treated with antibiotics 62% longer and symptoms associated with urethral syndrome 33% longer. Symptom duration was shorter if the doctor was perceived to be positive about prognosis, and longer with frequent somatic symptoms, previous history of cystitis, urinary frequency and more severe symptoms at baseline. (4) 66% of the MSU group had laboratory-confirmed UTI. Women suffered 3.5 days of moderately bad symptoms if they took antibiotics immediately but 4.8 days if they delayed taking antibiotics for 48 hours. Taking bicarbonate or cranberry juice had no effect. (5) The MSU group was more costly over 1 month but not over 1 year. Cost-effectiveness acceptability curves showed that for a value per day of moderately bad symptoms of over £10, the dipstick strategy is

most likely to be cost-effective. (6) Fear of spread to the kidneys, blood in the urine, and the impact of symptoms on vocational and leisure activities were important triggers for seeking help. When patients are asked to delay taking antibiotics the uncomfortable and worrying journey from 'person to patient' needs to be acknowledged and the rationale behind delaying the antibiotics made clear.

Conclusions: To achieve good symptom control and reduce antibiotic use clinicians should either offer a 48-hour delayed antibiotic prescription to be used at the patient's discretion or target antibiotic treatment by dipsticks (positive nitrite or positive leucocytes and blood) with the offer of a delayed prescription if dipstick results are negative.

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List of abbreviations

ASM	American Society of Microbiology	NCCHTA	National Coordinating Centre for Health Technology Assessment
CEAC	cost-effectiveness acceptability curve	NPT	near patient tests
cfu	colony-forming unit	NPV	negative predictive value
CI	confidence interval	OR	odds ratio
HTA	Health Technology Assessment	OTC	over-the-counter
IRR	incidence rate ratio	PPV	positive predictive value
LR	likelihood ratio	PSSRU	Personal Social Services Research Unit
MSU	mid-stream specimen of urine	UTI	urinary tract infection

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objectives

- To estimate independent clinical and dipstick predictors of infection and develop clinical scores.
- To test the clinical scores in an independent sample.
- To understand the natural history of urinary tract infection (UTI) and its key determinants.
- To perform a randomised controlled trial comparing management using the clinical and dipstick score with commonly used alternative management strategies.
- To estimate the resource use associated with each management strategy and estimate cost-effectiveness.
- To understand women's understanding of and concerns about the presentation and management of UTI, and particularly their responses to being asked to delay antibiotics.

Design

Six studies were carried out:

- a validation development study for diagnostic clinical score and diagnostic dipstick score (training study)
- a validation study for scores developed in study 1 (testing study)
- an observational study of the natural history of UTI
- a randomised controlled trial of scores developed in study 1
- an economic analysis of the randomised controlled trial
- a qualitative study of patients in the randomised controlled trial.

Setting

The setting was primary care.

Subjects

In total, 427 women aged 17–70 with suspected UTI participated in study 1; 434 participated

in study 2; 843 participated in study 3; 309 participated in the randomised controlled trial; and 21 participated in the qualitative study.

Methods

Validation studies

Independent clinical and dipstick predictors were estimated for diagnosis based on the European urinalysis guidelines standards for bacteriuria.

Observational study

Independent predictors of symptom severity and duration were estimated.

Randomised controlled trial

Patients were randomised to five basic management approaches:

- empirical antibiotics
- empirical delayed antibiotics (by 48 hours)
- target antibiotics based on a higher symptom score (two or more of urine cloudiness, smell, nocturia, dysuria)
- target antibiotics based on dipstick results (nitrite or both leucocytes and blood)
- target antibiotics based on receipt of a positive mid-stream specimen of urine (MSU) result.

Advice on self-care was also controlled by randomisation.

Qualitative study

A total of 21 participants from the trial participated in a recorded semistructured interview, which was analysed using the constant comparative method.

Economic study

NHS resource use was estimated using data in GP notes, and effectiveness was estimated by the number of days for which symptoms were rated as moderately bad by patients.

Results

The validation development study

In total, 62.5% of women had confirmed UTI (i.e. symptoms suggestive of UTI and bacteriuria). Only nitrite, leucocyte esterase (+ or greater) and blood (haemolysed trace or greater) independently predicted diagnosis (multivariate odds ratios 6.36, 4.52 and 2.23 respectively). A dipstick rule – based on having nitrite or both leucocytes and blood – was moderately sensitive (77%) and specific (70%) [positive predictive value (PPV) 81%, negative predictive value (NPV) 65%]. Predictive values were improved by varying the cut-point: the NPV was 73% for all three dipstick results being negative, and the PPV was 92% for having nitrite and either blood or leucocyte esterase. A clinical rule – based on having two of urine cloudiness, offensive smell, reported moderately severe dysuria and moderately severe nocturia – was less sensitive (65%) (specificity 69%, PPV 77%, NPV 54%). The NPV was 71% for none of the four clinical features and the PPV was 84% for three or more features.

The validation testing study

In total, 66% of women had confirmed UTI. The predictive values of nitrite, leucocyte esterase (+ or greater) and blood (haemolysed trace or greater) were confirmed (independent multivariate odds ratios of 5.56, 3.49 and 2.12 respectively). The dipstick rule – based on the presence of nitrite or both leucocytes and blood – was moderately sensitive (75%) but less specific (66%) (PPV 81%, NPV 57%). Predictive values were improved by varying the cut-point: the NPV was 76% for all three dipstick results being negative, and the PPV was 92% for having nitrite and either blood or leucocyte esterase.

Urine offensive smell was not found to be predictive in this sample; for a clinical score using the remaining three predictive clinical features (urine cloudiness, dysuria and nocturia) the NPV was 67% for none of the features and the PPV was 82% for three features.

The observational study of the natural history of urinary tract infection

Women in this study were nested in studies 1 and 2. A total of 684 women provided symptom information and 511 had both laboratory results and complete diaries. Symptoms rated by the patient as a moderately bad problem or worse

lasted an average of 3.25 days for infections sensitive to antibiotics. After adjusting for other predictors, when compared with sensitive infections, resistant infections lasted 56% longer [95% confidence interval (CI) 22–99%, $p < 0.001$], those with no antibiotic treatment 62% longer (95% CI 13–131%, $p = 0.008$) and those associated with urethral syndrome 33% longer (95% CI 14–56%, $p < 0.001$). Symptom duration was shorter if the doctor was perceived to be positive about diagnosis and prognosis and longer with frequent somatic symptoms, a previous history of cystitis, urinary frequency and more severe symptoms at baseline. Infections with no antibiotic treatment and also antibiotic-resistant infections were also associated with more severe frequency and dysuria symptoms after presentation.

The randomised trial

In total, 66% of the MSU group had laboratory-confirmed UTI – i.e. similar to the validation and observational studies. There were differences in antibiotic use between antibiotic management groups (immediate antibiotics 97%, MSU 81%, dipstick 80%, symptom score 90%, delayed antibiotics 77%, likelihood ratio test $p = 0.011$) and also in the use of MSUs at the initial consultation (23%, 89%, 36%, 33% and 15% respectively, $p < 0.001$), but little difference in symptomatic outcomes. Women suffered 3.5 days of moderately bad symptoms if they took antibiotics immediately. Those commencing antibiotics after 48 hours subsequently reconsulted less (hazard ratio 0.57, 95% CI 0.36–0.89) but also suffered a 37% longer duration of symptoms (95% CI 11–68%, $p = 0.003$), mainly in the MSU group (70% longer duration; other groups $\leq 21\%$ longer duration). Advice to use bicarbonate or cranberry juice had no effect on any outcome.

The economic analysis

The MSU group was more costly over a period of 1 month but not over a period of 1 year. There were modest non-significant differences in the estimates of effectiveness. To allow for the uncertainty of estimates we estimated cost-effectiveness acceptability curves for the strategies, which suggest that if a day of moderately bad symptoms is given a low value, i.e. less than approximately £10, then immediate antibiotics is likely to be the most cost-effective strategy. For values over £10 the dipstick strategy becomes the most likely to be cost-effective. Because of the uncertainty we can never

be more than 70% certain that the dipstick strategy is the most cost-effective.

The qualitative study

Several important features associated with women's health-seeking behaviour and their experiences of consulting for a UTI were identified, as well as their general attitudes towards and understanding of UTI, its aetiology and treatment. A fear of spread to the kidneys and the appearance of blood in the urine were two organic symptoms that particularly triggered worry and, in turn, seeking help. The generalised impact of symptoms on vocational and leisure activities was considerable and women expressed these as important triggers for seeking help. When patients are asked to delay taking antibiotic medication, i.e. they are essentially asked to 'wait some more', the sometimes protracted, uncomfortable and worrying journey that people have taken from 'person to patient' needs to be acknowledged. Some patients who had negative experiences of delay indicated that they had not felt validated in their expressions of bodily change and were threatened by such delay because, it seemed, the rationale for not taking the antibiotics was unclear.

Conclusions

- A clinical score is of limited value in increasing diagnostic precision, and dipstick results modestly improve diagnostic precision, but both of these diagnostic strategies have poor NPVs; they should not be used to rule out infection.
- Being positive about the diagnosis and natural history for patients with suspected UTI may help symptom resolution, and doctors can provide useful information on the natural history for patients (patients with a past history and those with high somatisation and severe

baseline symptoms will have more severe symptoms lasting longer than 3 days).

- Immediate antibiotics targeted using dipsticks with a delayed prescription as backup or an empirical delayed prescription both achieve similar symptom control to immediate antibiotics and reduce antibiotic use.
- Dipsticks are likely to be cost-effective if the value of saving a day of moderately bad symptoms is valued at £10 or more, but caution is required given the considerable uncertainty surrounding the estimates.
- If women are asked to delay taking antibiotics, great care is needed in both acknowledging the triggers to consult and particular worries and explaining the rationale for not using antibiotics immediately.

Implications for practice

Although all of the strategies trialled are acceptable, to both achieve good symptom control and reduce antibiotic use clinicians should probably either offer a 48-hour delayed antibiotic prescription to be used at the patient's discretion or target antibiotic treatment by dipsticks (positive nitrite or positive leucocytes and blood) with the offer of a delayed prescription if dipstick results are negative.

Suggestions for research

- Trials are needed of alternative diagnostic approaches (e.g. microscopy, dipsticks combined with dipslides).
- Further research is needed to estimate quality of life and model cost-effectiveness of the different strategies.
- More research is needed into the use of alternatives/complements to antibiotics (e.g. herbal medicines).

Chapter I

Developing clinical scores to predict urinary tract infection in primary care settings

Introduction

Acute urinary tract infection (UTI) is one of the commonest acute bacterial infections among women.^{1,2} Conventional diagnosis relies on identifying a potential urinary pathogen from culture of a mid-stream specimen of urine (MSU) in a symptomatic patient. The standard for reporting in most previous research and clinical practice was 10^5 colony-forming units per ml (cfu/ml);³ however, lower colony counts are associated with symptoms and respond to treatment,⁴ only 5% of low counts remit, the rest remain symptomatic, and 50% progress to high counts with symptoms.^{5,6} However, although both the American Society of Microbiology (ASM) and European urinalysis guidelines have recently recommended reporting much lower colony counts⁶ (10^3 and 10^2 cfu/ml respectively), little research has used these standards.

In clinical practice the universal use of MSUs is probably not cost-effective; empirical antibiotic treatment is advocated.⁷ However, the problem with universal antibiotic use is the growing problem of antibiotic resistance^{8,9} (now 20% of laboratory specimens). Thus, a key question is whether we can use history and physical examination, or near patient tests (NPTs), for better diagnosis and the targeting of antibiotics?

Symptoms

A recent systematic review³ identified nine studies that related symptoms and signs to diagnosis; however, it documented significant limitations:

- The authors identified few studies with ≥ 50 consecutive patients or independent blind comparison of symptoms and signs with a gold standard among patients with suspected UTI – in particular, none in primary care; 50 patients are also much too few to be adequately powered for symptom prevalences of 20–70%.

- The predictive value depended on setting (e.g. secondary care) and inclusion (e.g. some studies included suspected vaginal infection)
- Only one study – rated poorly methodologically – assessed the predictive value of combining symptoms.
- None explored the implications of the severity of reported symptoms nor used recent diagnostic standards.⁶

Near patient tests

Dipsticks are the most widely used simple NPT in primary care.^{10–13} Summary data are available of studies that assessed nitrite and leucocyte esterase separately, but primary data are needed to assess the independent predictive value of all dipstick results.¹⁴ A systematic review suggested that the evidence base for dipstick use in primary care is poor because of the paucity of studies and ‘spectrum bias’.^{13,15,16} Studies from primary care have a range of one or more limitations:^{9,11,15–19} they have not assessed the independent value of dipstick results and symptoms (hence potentially overcomplicating clinical decision rules); they have not used the range of dipstick variables (most include nitrite and leucocyte but not blood); they have failed to develop and then test algorithms in separate samples (the study by McIsaac *et al.*¹⁹ being the exception); and/or they have low power. Only the most recent dipstick studies^{17,19} have used the recent more rigorous laboratory guidelines for diagnosis. Evidence from emergency settings suggests that dipsticks may be particularly helpful when clinical assessment indicates an intermediate probability of infection.¹⁷

An adequately powered study was therefore needed:

- among women presenting in primary care with suspected UTI

- to assess the independent predictive value of symptoms, all dipsticks results and their combination
- to develop the simplest possible clinical scoring methods for clinicians to remember by determining the most predictive variables using multivariate methods
- to use more sensitive laboratory gold standards.

Methods

Setting

Between April 2002 and May 2003, 117 doctors or practice nurses from 67 practices in the south of England recruited 427 patients following informed written consent. Most doctors/nurses recruited only a few patients before stopping recruitment.

Inclusion criteria

Adult female patients (aged 18 and over) in whom UTI was suspected – usually patients with a history of dysuria and frequency.

Exclusion criteria

Patients for whom other diagnoses were considered likely, e.g. women with vaginal symptoms.³ Also men, children, pregnancy, age over 70^{20–24} and current severe mental problems (e.g. dementia).

Data collection

Structured clinical information was recorded by the clinician at the time of consultation (*Table 1*). Patients were asked to rate each symptom as a slight problem, a moderately severe problem or a severe problem.^{25,26} Patients were asked to provide a clean-catch MSU (no instructions were given

regarding cleaning or parting the labia). The doctor or nurse documented whether an MSU was cloudy to the naked eye or smelled offensive¹¹ and was instructed to perform a dipstick test (which was read manually) during the consultation using Bayer 8 SG strips according to the manufacturer's instructions. Other than a brief explanation of data collection procedures no special training in the use of dipsticks was given.

Laboratory analysis

The MSU was transported as in routine practice and 10 µl of MSU specimen was cultured onto cystine lactose electrolyte deficient (CLED) agar and incubated overnight at 37°C.

Rationale for diagnosis

We assume that laboratory evidence of bacterial growth combined with symptoms suggestive of UTI is the best evidence of infection,^{4,6} and that recent reports of intracellular infection remain of uncertain diagnostic significance.²⁷ The ASM guidelines suggest reporting down to 10² cfu/ml of *Escherichia coli*, whereas European urinalysis guidelines, while acknowledging the case for the lower cut-off, conclude that the most appropriate cut-off balancing sensitivity and specificity is down to 10³ cfu/ml⁶ for pure growth of *E. coli* but higher counts for more unusual organisms or mixed growths.⁶ We therefore used the European urinalysis guidelines but have also reported the results with the standard of 10⁵ cfu/ml used in the vast majority of previous evaluations of symptoms, signs and dipsticks.³

Postal questionnaire

This documented demographics and past history (including past history of UTI).

TABLE 1 Dipstick clinical decision rule performance in predicting diagnosis of urinary tract infection (UTI) according to European urinalysis guidelines standards^a

Standard	Test		
	Dipstick rule –	Dipstick rule +	Total
UTI –	108	46	154
UTI +	58	196	254
Total	166	242	

^a The dipstick decision rule is based on having either nitrite or blood and leucocytes. Dipstick + = nitrite or blood and leucocytes; dipstick – = neither nitrite nor blood and leucocytes combined.
Sensitivity = 196/254 = 77.2% (95% CI 72.0–82.4%); specificity = 108/154 = 70.1% (62.9–77.3%); PPV = 196/242 = 81.0% (76.1–85.9%); LR +ve test = 2.58 (2.01–3.32); LR –ve test = 0.33 (0.25–0.42).

Sample size (alpha = 0.05; beta = 0.2; nQuery Advisor sample size programme)

Assuming that 50% of urine samples are infected⁸ and that the prevalence of predictive variables is 20–70%, to detect an odds ratio (OR) of 2 required 403 patients. For sensitivities and specificities of between 50% and 80%, 400 patients will estimate sensitivity or specificity with 95% confidence intervals (CIs) of $\pm 6\text{--}7\%$. This sample size calculation was agreed with the National Coordinating Centre for Health Technology Assessment (NCCHTA) given that our original target was to achieve tighter estimates for the CIs; 95% CIs of $\pm 5\%$ would require 770 complete results.

Analysis

Developing clinical scores

We dichotomised and ordered categorical variables – using cut-offs for an OR of 2 or close to 2 and using similar cut-offs for different symptoms to simplify any resultant clinical score. In multivariate logistic regression we entered significant variables stepwise and retained them if still significant at the 5% level and with ORs of 2 or near 2. Finally, all other variables were checked. We computed scores based on simple counts of the rounded logistic coefficients using the coefficients from each separate model that we developed for each score (a clinical model, a dipstick model and a combined model) and determined the receiver operator curve for each score.

Developing clinical prediction rules

The performance of each score for different cut-offs in the score was assessed to develop the best cut-point for a clinical prediction rule. At each cut-off we determined the sensitivity, specificity, positive and negative predictive values, likelihood ratios for a positive test [LR +ve test; sensitivity/(1-specificity)], likelihood ratios for a negative test [LR -ve test; (1-sensitivity)/specificity] and the number above the cut-off.

Results

Study population

Fewer than 5% of eligible patients approached declined to participate. Of the 427 who agreed to

participate, for 408 (96%) both clinical information and laboratory tests were available. Comparing patients from GPs/nurses who recruited more than 10 patients ('high recruiters'; $n = 162$) with those from 'lower recruiters' ($n = 246$) there was no significant difference in the number with a diagnosis of UTI (65% versus 61%) nor dipstick results, which suggests that major selection bias is unlikely.

The median time between test and standard was 6 hours. The time between test and standard did not predict the finding of bacteriuria (OR for time in hours 1.01, 95% CI 0.99–1.02, $z = 0.95$, $p = 0.34$).

In total, 177/408 (43%) had high colony counts ($\geq 10^5 \text{ cfu/ml}$) and 254/408 (62%) the more rigorous criteria of low colony counts ($\geq 10^3 \text{ cfu/ml}$) according to European guidelines.⁶

A total of 270/408 (63%) returned the demographic questionnaire; there were no significant differences between those who did and those who did not return the questionnaire (diagnosis of UTI 65%, 58%; nitrite 20%, 18%; leucocytes 74%, 66%; urine cloudy 38%, 34%; moderately severe dysuria 60%, 60% respectively). Of these 270 participants, 195 (72%) reported a previous UTI, 150 (56%) were married, 174 (64%) were in employment or at college and 172 (64%) reported having some educational qualifications – similar to national attending samples.²

Dipsticks (Table 2)

Three variables independently predicted diagnosis: nitrite was most predictive followed by leucocytes and blood. A cut-off of 2 or more in a score based on the sum of the rounded logistic coefficients – equivalent to a clinical decision rule based on patients having either nitrite or leucocyte and blood – had a sensitivity of 77% and a specificity of 70% (Tables 1 and 3). Each end of the score could be used to improve performance, i.e. by varying the cut-point. Thus, the negative predictive value (NPV) was 73% (LR -ve test 0.22) for having none of dipstick nitrite, blood or leucocyte esterase, and the positive predictive value (PPV) was 92% (LR +ve test 7.2) for having nitrite and either blood or leucocyte esterase (Table 3).

Clinical variables

Four variables independently predicted UTI (Table 4) – cloudy urine, smelly urine and dysuria and/or nocturia as a moderately severe problem. Severity

TABLE 2 Dipstick predictors of diagnosis of urinary tract infection (UTI) according to European guidelines standards

	UTI, n (%)	No UTI, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)^a	p-value
<i>n</i>	254	154			
Nitrite	72 (28)	7 (9)	8.31 (3.71–18.6)	6.36 (2.77–14.6)	< 0.001
Leucocyte (+ or greater)	217 (85)	72 (47)	6.68 (4.17–10.7)	4.52 (2.72–7.50)	< 0.001
Blood (haemolysed trace or greater)	186 (73)	71 (46)	3.20 (2.10–4.87)	2.23 (1.38–3.61)	< 0.001
Protein (+ or greater)	119 (47)	47 (31)	2.00 (1.32–3.06)	1.12 (0.69–1.83)	0.643

^a Adjusted mutually for other variables in the model (nitrite, leucocyte and blood).

was important: symptoms rated as a slight problem were much less predictive. A cut-off of 2 or more in a score based on the sum of the rounded logistic coefficients – i.e. a clinical decision rule based on two out of four features – had a sensitivity of 65% and a specificity of 69% (*Tables 5 and 6*). Each end of the score could be used to improve performance, i.e. by varying the cut-point. Thus, the NPV was 71%, for none of the four clinical features and the PPV was 84% for three or more features (*Table 6*).

Implications of other approaches

The performance of the scores was not improved by combining dipstick and clinical variables, by using a sequential approach to the use of dipsticks (reserving dipsticks for those with intermediate

clinical scores) or by using a different laboratory standard (see Appendix 1).

Discussion

Summary of main findings

This study shows both the potential and the limitations of using dipstick and clinical information in practice to predict diagnosis. We developed a dipstick decision rule – based on having nitrite or both leucocytes and blood – that was moderately sensitive (77%) and specific (70%) but with a moderately low NPV (65%). The predictive values were improved by varying the cut-point: the NPV was 73% for all three dipstick results being negative, and the PPV was 92% for having nitrite and either blood or leucocyte

TABLE 3 Dipstick score to predict diagnosis of urinary tract infection using European guidelines standards^a

Cut-point (% at or above cut-point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified (%)	LR +ve test	LR -ve test
≥0 (100)	100	0			62.25	1	
≥1 (83) B	92.52	33.77	69.73	73.24	70.34	1.40	0.22
≥1.5 (73) L	87.80	51.95	75.08	72.07	74.26	1.83	0.23
≥2 (59) B+L or N	77.17	70.13	80.99	65.06	74.51	2.58	0.33
≥3 (19) N+B	27.95	96.10	92.22	44.71	53.68	7.17	0.75
≥3.5 (17) N+L	25.98	96.75	92.96	44.21	52.70	8.00	0.77
≥4.5 (12) N+L+B	17.72	98.05	93.75	41.94	48.0	9.09	0.84
> 4.5 (0)	0	100			37.75		1

^a Score weighted according to the rounded logistic coefficients: sum of nitrite (N) = 2, leucocyte (L) = 1.5, blood (B) = 1. The score was robust to weighting assumptions: there was a similar performance for an unweighted score or for a score weighted according to the odds ratios.

The score gave an area under the receiver operator curve of 0.78 (95% CI 0.74–0.83).

TABLE 4 Clinical predictors of diagnosis of urinary tract infection (UTI) according to European guidelines standards

	UTI, n (%)	No UTI, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)^a	p-value
<i>n</i>	254	154			
Urine cloudy on examination	117 (46)	32 (21)	3.26 (2.05–5.16)	2.32 (1.40–3.85)	0.001
Urine offensive smell on examination	62 (24)	16 (10)	2.79 (1.54–5.03)	2.02 (1.05–3.90)	0.034
Patient reports dysuria a moderately severe problem	179 (70)	66 (43)	3.18 (2.10–4.83)	2.76 (1.78–4.28)	< 0.001
Patient reports nocturia a moderately severe problem	137 (54)	56 (36)	2.05 (1.36–3.09)	1.81 (1.16–2.80)	0.008
Patient reports daytime frequency a moderately severe problem	185 (72)	94 (61)	1.71 (1.12–2.62)	1.37 (0.85–2.22)	0.20
Patient reports urgency a moderately severe problem	158 (62)	77 (50)	1.65 (1.10–2.47)	1.01 (0.63–1.61)	0.97
Patient reports haematuria a moderately severe problem	59 (23)	18 (12)	2.29 (1.29–4.05)	1.71 (0.93–3.16)	0.085

a Other variables tested but not significant in either univariate or multivariate analysis: history of backache, fever, feeling unwell, abdominal pain, previous duration, daytime or night-time frequency (number of times), renal angle tenderness, lower abdominal tenderness, previous history of UTI.

esterase. A clinical rule was also developed – based on having two of urine cloudiness, offensive smell, reported moderately severe dysuria and moderately severe nocturia – but was less sensitive (65%) with a lower NPV (54%). The predictive value of the clinical rule could also be improved by modifying the cut-point: the NPV was 71% for none of the four clinical features and the PPV was 84% for three or more features. When using these rules in

practice, clinicians will need to use appropriate strategies to take account of the relatively low NPVs.

Strengths and limitations

Strengths

This is the first adequately powered study to assess the independent predictive value of dipstick results

TABLE 5 Clinical rule performance in predicting diagnosis of urinary tract infection (UTI)^a

Standard	Test		Total
	Clinical rule –	Clinical rule +	
UTI –	106	48	154
UTI +	90	164	254
Total	196	212	

a The clinical decision rule is based on having two or more of moderately bad dysuria, moderately bad nocturia, urine smell offensive, urine cloudy. Clinical rule + = two or more of moderately bad dysuria, moderately bad nocturia, urine smell offensive, urine cloudy or nitrite, or leucocyte and blood. Clinical rule – = one or less of moderately bad dysuria, moderately bad nocturia, urine smell offensive, urine cloudy or nitrite, or leucocyte and blood.
Sensitivity = 164/254 = 64.6% (95% CI 58.7–70.5%); specificity = 106/154 = 68.8% (61.5–76.1%);
PPV = 164/212 = 77.4% (71.8–83.0%); LR +ve test = 2.07 (1.61–2.66); LR -ve test = 0.51 (0.42–0.63).

TABLE 6 Clinical score to predict diagnosis of urinary tract infection using European guidelines standards^a

Cut-point (% at or above cut-point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified (%)	LR +ve	LR -ve
≥ 0 (100)	100	0			62.25	1.00	
≥ 1 (83)	92.13	31.17	68.82	70.59	69.12	1.34	0.25
≥ 2 (52)	64.57	68.83	77.36	54.08	66.18	2.07	0.51
≥ 3 (23)	30.71	90.26	83.87	44.13	53.19	3.15	0.77
≥ 4 (5)	7.48	99.35	95.00	39.43	42.16	11.52	0.93
> 4 (0)	0.00	100			37.75		1.00

^a Score weighted according to the rounded logistic coefficients: sum of urine cloudiness = 1, urine smell = 1, moderately severe dysuria = 1, moderately severe nocturia = 1.

The predictive value of the clinical score with the four independently predictive variables had an area under the receiver operator curve of 0.71 (95% CI 0.67–0.76). Including a history of any haematuria – i.e. using a different cut-off for haematuria compared with other symptoms, and at the expense of greater complexity – slightly improved the sensitivity of the clinical score: a score of two or more out of the five variables (62% of the sample) had a sensitivity of 75% (191/254), specificity of 61% (94/154), PPV of 76% (191/251), NPV of 60% (94/157), LR +ve test of 1.93 and LR -ve test of 0.41.

and symptoms in a primary care sample. The sample had similar characteristics to UK national attending samples² and a similar incidence of UTI to previous primary care studies.¹⁸ We also chose the recommended group, i.e. those patients in whom UTI was the suspected diagnosis.³

Limitations

The results may not apply to other groups (e.g. when either vaginal or urinary infection is suspected³). There was variability in transit time but there was no evidence that this affected the likelihood of bacteriuria. As with any reference standard there will be false-negative and false-positive results. If intracellular infection²⁷ is common and relevant then neither the reference standard nor the test (dipstick) may be sensible. Serial MSUs might have limited the error but this was less pragmatic, was potentially confounded by antibiotic treatment and might have reduced recruitment. Although we have used multiple variables in developing the models, type I error is less likely as the results were highly significant for most variables. We have also estimated the performance of the clinical rules in the same population; further prospective validation is required.

Comparison with the existing literature

Four clinical variables independently predicted diagnosis. To our knowledge, this study is the only adequately powered level 1 study to date among women with presumed UTI to identify the

independent predictive value of symptoms,³ which uses lower colony count as the gold standard.⁶ We could not confirm the findings of a moderate-sized study¹⁹ ($n = 231$) in primary care that duration of symptoms for 1 day predicted diagnosis.

Key findings were:

- Symptom severity may be important – simply the presence of symptoms³ was less predictive.
- A simple examination of the urine for cloudiness or smell provides important information.¹¹
- The use of low colony counts provides a ‘better gold standard’. Predictive values were better when lower colony counts were included in the gold standard, which supports the validity of lower counts;⁶ if low colony counts were spurious, i.e. providing non-differential measurement error, predictive values would be worse when low colony counts were included as part of the gold standard.

Three key dipstick variables independently predict diagnosis, i.e. nitrite, leucocytes and blood, and a dipstick rule performed slightly better than a clinical rule. Previous studies in primary care have either had limited power¹⁹ or not assessed the independent value of dipstick results using multivariate analysis.^{11,13,14,18} These findings demonstrate the importance of multivariate analysis and contradict previous findings about protein,¹⁸ which does not independently predict UTI. Dipsticks have the potential to target treatment and to have lower costs depending on

the precise strategy used. However, the results also suggest significant limitations in the performance of urinanalysis,^{10,13,15–17} particularly low NPVs.

Implications for clinical practice

Given the current debate about the appropriateness of antibiotics for uncomplicated UTI²⁸ there is also likely to be ongoing controversy over how to use any clinical or dipstick decision rules. The main limitation is the number of women with UTI that are ‘missed’ – in this study 35% ($n = 90$), of whom 38% ($n = 34$) had low colony counts for the clinical rule. How much does this matter? We know that most women with symptoms of cystitis do not contact a health professional and can treat themselves conservatively,^{1,29,30} and the placebo groups of randomised controlled trials suggest that women not treated with antibiotics mostly get better (albeit more slowly), suffer complications rarely and will not suffer greater recurrence.^{28,31} Thus, the utility of a clinical decision rule is not that it can perfectly target antibiotics (which is not strictly necessary) but that it can target antibiotics more appropriately than either empirical treatment or self-management, and that it is less likely to encourage belief in the importance of seeing the doctor than in routinely performing MSUs in all patients.³² A clinical rule could also be potentially useful as part of telephone- or internet-based triage. Given the moderately low sensitivity of the rule, a reasonable approach would be to advise women who have less than two of the four features to return if their symptoms are not settling with conservative treatment, or, alternatively, to offer a backup (delayed) prescription of antibiotics, as used for respiratory infection.^{33,34} Similarly, for

dipsticks, a reasonable approach would be to ask women with negative dipstick results to return if their symptoms are not settling, or to provide a delayed prescription. Such pragmatic strategies require further testing in randomised controlled trials.

Maximising predictive value: varying the cut-points

Clinicians may wish to vary the threshold for empirical management using the cut-points at either extreme of the clinical scores (see Appendix 1). Thus, for dipsticks, for patients with neither nitrite, blood or leucocytes, UTI is unlikely (NPV 73%; LR –ve test 0.22) and symptomatic advice and/or a delayed prescription would be reasonable; for those with nitrite and either blood or leucocytes, UTI is very likely (PPV 92%; LR +ve test 7.2) and empirical antibiotics are sensible; the remaining patients could be targeted for either investigation and/or a delayed prescription. A similar strategy could be used for the clinical score, with symptomatic advice for patients having none of the four features (NPV 71%) and empirical antibiotics for those with three or more features (PPV 84%).

Conclusion

Simple decision rules could improve targeting of investigation or treatment, but strategies to use such rules need to take account of their limited NPV. Further research is needed to confirm the validity of these findings in a separate sample.

Chapter 2

Validating clinical scores to predict urinary tract infection in primary care settings

Introduction

The previous chapter reported a validation development study in which a clinical score and a dipstick score were developed based among women presenting in primary care with suspected UTI. The predictive value of any scoring system that is tested in the same sample used to compute the scoring system is likely to have artificially inflated predictive values; therefore, both a training and a validation set are needed. To estimate the more realistic predictive values of these scores, we assessed the predictive value of their components and of the scores in a new validation sample.

Methods

Setting

Between January 2002 and February 2005, 117 primary care clinicians (doctors or practice nurses) from 62 practices in the south of England recruited 434 patients following informed written consent. The clinicians recruited consecutive patients and most recruited only a few patients before stopping recruitment.

Data collection, inclusion criteria, laboratory analysis and questionnaires

These were the same as in Chapter 1.

Sample size (alpha = 0.05; beta = 0.2; nQuery Advisor sample size programme)

Assuming that 50% of urine samples are infected¹⁸ and that the prevalence of predictive variables is 20–70%, to detect an OR of 2 required 403 patients. For sensitivities and specificities of between 50% and 80%, 400 patients estimates sensitivity or specificity with 95% CIs of $\pm 6\text{--}7\%$ (to achieve $\pm 5\%$ would require 770 complete results).

Analysis

We assessed the variables found to be predictive from the previous study in multivariate logistic regression. We also assessed the previously developed clinical scores by cross-tabulation, computed any new scores based on simple counts of the rounded logistic coefficients and determined the receiver operator curve for each score. The performance of each score for different cut-offs in the score was assessed. At each cut-off we determined the sensitivity, specificity, PPV and NPV, LR +ve test; sensitivity/(1-specificity), LR -ve test; (1-sensitivity)/specificity, and the number above the cut-off.

Results

Study population

More than 90% of eligible patients agreed to participate. Of the 434 who agreed to participate, dipstick information was available for 429 (99%) and clinical information for 431 (99%). In total, 219 (50%) participants were found to have high colony counts ($\geq 10^5 \text{ cfu/ml}$) and 287 (66%) the more sensitive criteria of lower colony counts ($\geq 10^3 \text{ cfu/ml}$) according to European urinalysis guidelines.⁶ Of the 269 patients who returned the demographic questionnaire, 200 (74%) reported a previous UTI, 152 (57%) were married and 152 (57%) were reported as having an educational qualification of at least one GCSE or equivalent.

Assessing the predictive value of dipstick variables

Nitrites were found to be most predictive, followed by blood and then leucocytes (based on leucocyte esterase) (Table 7), with ORs very similar to those in the previous derivation study. The previously developed dipstick rule – based on having nitrite or both leucocytes and blood – was moderately sensitive (75%, 95% CI 71–78%) but less specific

TABLE 7 Dipstick predictors of diagnosis of urinary tract infection (UTI)

	UTI, n (%)	No UTI, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)^a	p-value
Nitrite	98 (34.51)	9 (6.21)	7.96 (3.88–16.32)	5.56 (2.66–11.66)	<0.001
Leucocyte (+ or greater)	246 (86.62)	77 (53.10)	5.72 (3.56–9.17)	3.49 (2.08–5.84)	0.002
Blood (haemolysed trace or greater)	205 (72.44)	61 (42.36)	3.57 (2.35–5.44)	2.12 (1.32–3.40)	<0.001
Protein (+ or greater)	158 (55.63)	47 (32.41)	2.61 (1.72–3.98)	1.22 (0.74–1.98)	0.433

^a Adjusted mutually for other significant variables in the model (nitrite, leucocyte and blood).

(66%, 95% CI 60–72%) (PPV 81%, 95% CI 77–84%; NPV 57%, 95% CI 52–62%). Predictive values were improved by varying the cut-point (*Table 8*): the NPV was 76% (95% CI 66–84%) for all three dipstick results being negative (cut-point ≥ 1), and the PPV was 92% (95% CI 86–96%) for having nitrite and either blood or leucocyte esterase (cut-point ≥ 3).

Clinical variables

Only two of the original four predictive variables that we found predicted bacteriuria from the derivation sample independently predicted UTI (*Table 9*) – cloudy urine and dysuria rated as a moderately severe problem. Moderately severe nocturia and offensive smell of urine were no longer significant. The original clinical decision rule from the derivation sample based on two or more of the above features was now found to have a sensitivity of 65% (95% CI 62–68%; previously

65%) and a specificity of 59% (95% CI 53–65%; previously 69%) (*Table 10*, cut-point ≥ 2). However, as the presence of nocturia to any degree was independently predictive (OR 1.60, 95% CI 1.01–2.55), we assessed a modified score so that simply the presence of the symptoms of nocturia and dysuria were included without the need for a severity rating; this resulted in increased sensitivity but still a poor NPV (*Table 11*); the NPV was 67% for none of the features and the PPV was 82% for three features.

Discussion

Summary of main findings

This study confirms both the potential and the limitations of using dipstick and clinical information in practice to predict diagnosis. The dipstick decision rule developed in the derivation sample (see Chapter 1) – based on having nitrite

TABLE 8 Validation of dipstick score to predict diagnosis of urinary tract infection (UTI)^a

Cut-point (% at or above cut-point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified (%)	LR +ve test	LR -ve test
≥ 0 (100)	100	0			66.28	1	
≥ 1 (84)	94.01	36.55	74.37	75.71	74.59	1.4817	0.1638
≥ 1.5 (77)	89.08	46.21	76.44	68.37	74.59	1.6561	0.2362
≥ 2 (61)	74.65	66.21	81.23	57.14	71.79	2.209	0.3829
≥ 2.5 (60)	73.59	66.90	81.32	56.40	71.33	2.2231	0.3948
≥ 3 (24)	33.45	94.48	92.23	42.02	54.08	6.0629	0.7044
≥ 3.5 (23)	32.04	94.48	91.92	41.52	53.15	5.8077	0.7193
≥ 4.5 (19)	25.70	95.17	91.25	39.54	49.18	5.3344	0.7806
> 4.5 (0)	0	100			33.80	1	

^a Score weighted according to the rounded logistic coefficients: sum of nitrite (N) = 2, leucocyte (L) = 1.5, blood (B) = 1.

TABLE 9 Clinical predictors of diagnosis of urinary tract infection (UTI)

	UTI, n (%)	No UTI, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)^a	p-value
Urine cloudy on examination	141 (49.30)	39 (26.90)	2.64 (1.71–4.08)	2.53 (1.62–3.93)	<0.001
Urine smell offensive on examination	82 (28.67)	28 (19.31)	1.68 (1.03–2.73)	1.18 (0.68–2.05)	0.556
Dysuria reported as a moderately severe problem	189 (66.08)	70 (48.28)	2.09 (1.39–3.14)	2.00 (1.31–3.04)	0.001
Nocturia reported as a moderately severe problem	133 (46.50)	64 (44.14)	1.10 (0.74–1.64)	0.99 (0.65–1.50)	0.959
Any nocturia	224 (78.32)	98 (67.59)	1.73 (1.11–2.71)	1.60 (1.01–2.55)	0.047

a Adjusted mutually for other variables in the model (cloudy urine, dysuria, night frequency). The estimate for any night frequency quoted above is adjusted for cloudy urine and moderately bad dysuria; if any night frequency and any dysuria are included in the model, for simplicity the estimates are cloudy urine 2.40 (1.54–3.75), night frequency 1.59 (1.00–2.53), dysuria 2.70 (1.64–4.44).

TABLE 10 Validation of clinical score to predict diagnosis of urinary tract infection (UTI)^a

Cut point (% at or above cut point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified (%)	LR +ve test	LR -ve test
≥0 (100)	100	0			66.36	1	
≥1 (86)	90.56	22.07	69.62	54.24	67.52	1.1620	0.4278
≥2 (57)	65.03	58.62	75.61	45.95	62.88	1.5171	0.5965
≥3 (24)	27.97	83.45	67.31	37.00	46.64	1.6900	0.8631
≥4 (6)	6.99	97.24	83.33	34.64	37.35	2.535	0.9565
>4 (0)	0	100			33.64	1	

a Score weighted according to the rounded logistic coefficients based on the sum of: urine cloudiness = 1, urine smell = 1, moderately severe dysuria = 1, moderately severe nocturia = 1.

TABLE 11 Clinical score based on cloudy urine/burning any degree/night frequency any degree^a

Cut point (% at or above cut point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly Classified (%)	LR +ve test	LR -ve test
≥0	100	0			66.36	1	
≥1 (96)	97.90	8.28	67.80	66.67	67.75	1.0674	0.2535
≥2 (71)	80.42	45.52	74.43	54.10	68.68	1.4761	0.4302
≥3 (29)	35.66	84.14	81.60	39.87	51.97	2.2484	0.7646
>3 (0)	0	100			33.64	1	

a Score weighted according to the rounded logistic coefficients based on the sum of: urine cloudiness = 1, burning dysuria any degree = 1, night frequency any degree = 1.

or both leucocytes and blood – was moderately sensitive but less specific in this sample than in the derivation sample; it also had a lower NPV (57%) than in the derivation sample. A clinical scoring system performed less well. Although the predictive values could be improved by varying the cut-points, the NPVs remained low. Thus, in practice, clinicians cannot rule out the diagnosis of UTI using either clinical information or dipstick results, and they will need to use appropriate strategies such as delayed prescription to take account of the relatively low NPVs.

Validation of a clinical decision rule and its use in practice

The previous clinical decision rules did not perform as well in this study as in this derivation sample. PPVs remained quite similar to those found in the derivation study, but NPVs were poor. Not all of the variables found to be predictive in the first study were as predictive in this study (urine smell was not found to be predictive in this sample). However, even using a modified score (*Table 11*) based on the variables confirmed to be predictive in this study (cloudiness, dysuria, nocturia) did not greatly improve the predictive values. The implications of this for practice are that clinicians can be reasonably confident that patients with suspected UTI who have dysuria, nocturia and cloudy urine do have UTI, but they should be cautious about excluding patients based on the absence of these features.

Validation of a dipstick decision rule and its use in practice

Three variables identified previously to be most independently predictive of UTI in the derivation

sample were tested in a new data set by multivariate analysis, and the multivariate ORs were similar to those in the previous study. The dipstick score performed better than the clinical score. At a cut-point in the score of greater than or equal to 2 (equivalent to having nitrite or both leucocytes and blood), both the sensitivity and the specificity of the score were very similar to those found previously, as was the PPV, but the NPV decreased from 65% (derivation sample) to 57% in this sample. Predictive values can be maximised by varying the cut-points in the score: with all three dipstick variables being negative it would be reasonable to say that a UTI would be unlikely (NPV 76%); however, even with this higher NPV, 24% of patients would be told that they have no UTI when in fact they do.

Conclusion

The pattern of clinical information in suspected UTI is of limited value in increasing diagnostic precision among patients with suspected UTI; although UTI is likely among patients with dysuria, nocturia and urine cloudiness, the absence of these features performs poorly in ruling out UTI. A dipstick rule modestly improves diagnostic precision but, in applying the results of dipsticks, clinicians will still need to take account of the limited NPVs, which are much lower than expected from previous research; even when all results are negative, 24% of women will still have UTI. This means that in practice clinicians should consider using strategies such as delayed prescribing for such patients^{33,34} – or alternatively advising a review consultation – if symptoms are not settling.

Chapter 3

The natural history of patients and the role of antibiotics and antibiotic resistance among patients presenting with suspected urinary tract infection in primary care

Background

The impact of antibiotic resistance

Laboratory data suggest that more than 20% of isolates are resistant to trimethoprim and cephalosporins and 50% to amoxicillin. There is recent evidence from the UK documenting the impact of antibiotic resistance in patients who were subsequently found to have UTI caused by *E. coli*, but symptom reporting was based on retrospective telephone assessment,³⁵ which limits the ability to assess the pattern and severity of symptoms. A recent prospective study using symptom diaries³⁶ has documented the association of antibiotic resistance with prolonged duration of milder symptoms (by 3 days: 7 versus 4 days), in which symptom resolution was defined as symptoms being labeled a very slight problem or less. However, patients and doctors may not alter prescribing decisions based on the duration of mild symptoms, and the impact of antibiotic resistance on more meaningful severe symptoms has not been documented. In addition, there have been no comparisons with untreated patients; however, it would be expected that the patterns observed would be similar to those seen in patients having antibiotics to which the infection is resistant. Finally, no observational study to date has both assessed and controlled for other factors that might strongly confound the assessment of symptom resolution (e.g. somatic symptom perception and health anxiety;³⁷ doctor consultation variables such as a positive approach to the problem^{38,39}).

The natural history

The very limited trial data suggest that uncomplicated UTIs have been shown to have a good long-term prognosis with a low risk of

renal damage and failure.⁴⁰ A Canadian study characterised the natural history of UTIs in primary care⁴¹ but was limited by the use of retrospective telephone interviews and its focus on patients treated with a 10-day course of ciprofloxacin (a second-line treatment; longer use than is normal in UK practice⁹). The study also did not provide information on the impact of antibiotic resistance or of not providing antibiotics. There is also paucity of data on the natural history of those presenting with suspected UTI but with no bacterial growth (i.e. so called 'urethral syndrome').

This study aimed to address these deficits by:

- describing the natural history of more severe symptoms in women presenting with suspected UTI in primary care, including those with confirmed UTI and those with urethral syndrome, and documenting the key demographic and consultation variables determining the duration and severity of symptoms
- assessing the impact of no treatment with antibiotics and of antibiotic resistance on symptom duration and severity whilst controlling for major potential confounding variables.

This study was not one of those commissioned by the HTA programme, but the data collected in studies 1 and 2 provided an invaluable data set to assess the role of antibiotics and other key variables in the natural history of UTI.

Method

This study was largely nested within the diagnostic studies described in Chapters 1 and 2.

Inclusion and exclusion criteria and laboratory analysis of urine specimens

These were as in studies 1 and 2.

Clinical date collection, and patient diary and questionnaire

The practitioner filled out a sheet of baseline symptoms and clinical information as well as demographic details of the patient (age, sex and postcode) and whether antibiotics were prescribed. Patients kept a daily record of symptoms, grading severity – 0 (no symptoms), 1 (a very slight problem), 2 (a slight problem), 3 (a moderately bad problem), 4 (a bad problem), 5 (a very bad problem) or 6 (as bad as it could be) – and took their temperature using a Tempa-DOT thermometer every night. The symptoms (dysuria, haematuria, frequency during day and night, ‘smelly urine’, ‘tummy pain’, generally feeling unwell and restriction of daily activities) were chosen based on the common presenting symptoms of UTI¹⁸ and were collected in a diary, the format of which has previously been validated and shown to be sensitive to change for other acute infections.²⁶ Patients were also phoned by the research assistant after 3 days to check that there were no problems with completing the diary. No questions were asked about compliance or a return to the surgery, as this could alter patient behaviour. On completion, patients returned their diaries to the research centre in a Freepost envelope. Patients also completed a questionnaire with the Somatic Symptom Inventory (a measure of somatisation)³⁷ and a questionnaire that measured patients’ perceptions of different aspects of communication in the consultation (a communication and partnership approach, interest in the patient’s life, a personal relationship, health promotion and a positive approach to diagnosis and prognosis).^{38,39} Patients’ perceptions of doctor communication were measured on a scale from 0 (very strongly disagree that the doctor did this) to 6 (very strongly agree).^{38,39}

Sample size (alpha = 0.05; beta = 0.2; nQuery Advisor sample size program)

If 20% of individuals have a resistant organism⁴ then a sample of 455 patients with complete outcomes will be able to detect a difference in symptom resolution of 0.33 standard deviations (1–2 days).

Analysis

We calculated means rather than medians because with small numbers medians are less sensitive to group differences. We assessed predictors of illness duration by negative binomial regression (because of overdispersion of the data). Linear regression was used for the symptom severity data. To assess potential confounding variables, variables significant in univariate analysis ($p < 0.05$) were entered into multivariate analysis and retained if they were significant; all of the univariate variables were then tested in the model and any further significant variables retained. To assess the pattern of symptoms in the period immediately after seeing the doctor when symptoms were most severe (days 2–4), we used factor analysis with varimax rotation and assessed the internal reliability of the scales using Cronbach’s alpha statistic.

Results

A total of 843 women took part, of whom 839 gave MSUs to their GP and 830 filled out baseline symptoms with their GP; 684 (81%) provided some information about symptom duration, and completed diaries were returned by 541 (64%). In total, 511 of these women had an antibiotic resistance status that could be classified (*Table 12*). The baseline characteristics of those women who were followed up and those who did not provide diary information were very similar for key symptoms (urgency, frequency, nocturia, dysuria), which suggests little response bias.

When an antibiotic was prescribed, a trimethoprim was used most frequently (> 80% of cases).

Pattern of symptoms

The mean duration of significant symptoms (defined as the duration of days when any symptom was rated moderately bad or worse) is shown in *Table 12*. The symptom rated most frequently as a moderately bad problem by patients was daytime frequency (78%), and more than 50% of patients also rated their dysuria, urgency and nocturia as a moderately bad problem or worse; 47% of patients were significantly unwell and 42% rated restriction of activities as a moderately bad problem or worse. Daytime frequency was the longest lasting symptom, but most other symptoms rated as a moderately bad problem lasted on average 3 days. Among patients in whom no UTI was confirmed (i.e. patients with so-called ‘urethral’ syndrome),

TABLE 12 Descriptive information: duration of symptoms after seeing the doctor/nurse (symptoms rated as a moderately bad problem)^a

		Duration (days)									
		Any symptom	Haematuria	Dysuria	Urgency	Daytime frequency	Nocturia	Offensive smell	Abdominal pain	Restricted activities	Unwell
n (%)	511	82 (16)	326 (64)	20 (63)	397 (78)	293 (57)	141 (28)	238 (47)	214 (42)	241 (47)	
Overall duration	3.83 (2.97)	1.88 (1.75)	2.67 (2.26)	3.06 (2.54)	3.46 (2.59)	3.14 (2.50)	2.92 (2.46)	3.15 (2.57)	2.89 (2.59)	3.13 (2.62)	
Antibiotic resistance											
Sensitive organism (n = 224)	3.32 (2.54)	1.78 (1.70)	2.24 (1.80)	2.48 (1.98)	3.03 (2.44)	2.52 (2.09)	2.13 (1.44)	2.61 (2.47)	2.68 (2.86)	2.71 (2.50)	
Unknown sensitivity (n = 47)	3.32 (2.06)	1.64 (1.50)	2.39 (2.89)	2.63 (1.87)	2.78 (1.73)	2.21 (1.59)	2.59 (1.54)	3.08 (2.36)	2.09 (1.11)	2.83 (1.72)	
Resistant organism (n = 40)	4.73 (2.91)	1.0 (0.0)	3.52 (2.06)	4.04 (2.47)	4.15 (2.22)	4.04 (2.22)	4.38 (2.61)	4.78 (3.41)	3.88 (3.26)	4.18 (2.94)	
UTI, no antibiotic given (n = 17)	4.94 (3.82)	3.00 (-)	5.25 (3.37)	4.71 (4.54)	6.3 (3.02)	4.22 (3.38)	6.00 (1.41)	2.20 (1.30)	5.17 (3.97)	5.33 (4.18)	
Urethral syndrome (n = 183)	4.30 (3.42)	2.35 (2.11)	3.08 (2.79)	3.63 (2.99)	3.81 (2.81)	3.97 (2.91)	4.21 (3.51)	3.50 (2.45)	2.99 (2.10)	3.29 (2.70)	

a This table includes only women for whom there was good-quality complete diary information for all symptoms and for whom the nature of antibiotic resistance could be determined (n = 511).

there was a similar pattern of severity of symptoms to those with confirmed UTI.

Duration of more severe symptoms: antibiotics, antibiotic resistance and other predictors

Compared with patients who had a sensitive organism, the duration of symptoms rated as moderately bad was 50–60% longer among patients with antibiotic-resistant organisms or when no antibiotic was given (*Tables 12 and 13*) when controlling for confounding variables (*Table 13*). The pattern observed would be predicted if antibiotics were effective in treating symptoms and antibiotic resistance was genuinely associated with adverse outcomes. The duration of symptoms rated as moderately bad was also less when the doctor was positive about diagnosis and when patients felt more enabled. Symptoms lasted longer with frequent somatic symptoms, past cystitis and with more severe symptoms at baseline. There was an inverse association between consultation variables (the doctor being positive and more enabling) and the total burden of moderately bad symptoms (*Table 14*).

Severity of symptoms

In the factor analysis of the severity of symptoms at day 1 two groups of symptoms were identified: a ‘frequency’ group of symptoms (increased day frequency, increased night frequency and urgency and dysuria) (Cronbach’s alpha 0.77) and an ‘unwell’ group of symptoms (abdominal pain, restricted activities and feeling unwell) (Cronbach’s alpha 0.80). At days 2–4 when symptoms remain the biggest problem there was a similar pattern (i.e. a frequency group and an unwell group of symptoms; Cronbach’s alpha 0.79 and 0.86 respectively). Antibiotic resistance and no antibiotic treatment were both associated with more severe frequency symptoms (i.e. dysuria, urgency, frequency and nocturia) (*Table 15*) but not as clearly with the unwell symptoms (*Table 16*) or the total number of moderately bad symptoms (*Table 14*).

Discussion

This study documents prospectively the natural history of the more severe symptoms for patients presenting with suspected UTI (i.e. including the urethral syndrome), and documents the roles of

TABLE 13 The relationship between antibiotic resistance and duration of moderate symptoms controlling for potential confounders using negative binomial regression

Sensitivity ^a	Univariate IRR (95% CI)	p-value	Multivariate IRR (95% CI)	p-value
Sensitive (mean 3.79 days)	1.00		1.00	
Unknown	1.00 (0.79–1.27)	0.996	1.03 (0.81–1.30)	0.833
Resistant	1.42 (1.12–1.81)	0.004	1.56 (1.22–1.99)	<0.001
No antibiotic	1.49 (1.06–2.10)	0.023	1.62 (1.13–2.31)	0.008
Urethral syndrome	1.29 (1.12–1.49)	<0.001	1.33 (1.14–1.56)	<0.001
Other predictors				
Positive approach to the natural history	0.93 (0.87–0.99)	0.020	0.91 (0.84–0.99)	0.021
Perceived personal relationship	1.04 (1.00–1.07)	0.043	1.05 (1.01–1.10)	0.016
Past cystitis	1.26 (1.09–1.46)	0.002	1.25 (1.07–1.46)	0.004
Somatic Symptom Inventory	1.04 (1.03–1.06)	<0.001	1.03 (1.01–1.05)	0.002
Severity of baseline unwell group of symptoms	1.11 (1.07–1.16)	<0.001	1.07 (1.02–1.12)	0.006
Daytime frequency (number of times)	1.01 (1.00–1.02)	0.008	1.01 (1.00–1.02)	0.005

a The sensitivity groups are compared with the sensitive group given antibiotics. If the complete data available for univariate analysis are used, the estimates are: unknown 1.00 (0.81–1.25); resistant 1.41 (1.14–1.75); no antibiotics 1.32 (0.97–1.81); urethral syndrome 1.29 (1.13–1.47). Other variables assessed were age leaving full-time education, marital status, the number of medical problems, perception of doctor communication (a communication and partnership approach, health promotion, interest in the effect on life) and health anxiety (Whitley Index).

TABLE 14 The relationship between antibiotic resistance and total symptom burden (total number of moderately bad symptoms) controlling for potential confounders using negative binomial regression

Sensitivity ^a	Univariate IRR (95% CI)	p-value	Multivariate IRR (95% CI)	p-value
Sensitive (mean 3.79 days)	1.00		1.00	
Unknown	1.10 (0.82–1.46)	0.535	1.15 (0.88–1.51)	0.313
Resistant	1.49 (1.10–2.02)	0.010	1.70 (1.27–2.26)	<0.001
No antibiotic	1.08 (0.69–1.70)	0.731	1.22 (0.75–1.98)	0.434
Urethral syndrome	1.20 (1.01–1.44)	0.040	1.39 (1.16–1.68)	<0.001
Other predictors				
Positive approach to the natural history	0.94 (0.87–1.01)	0.088	0.88 (0.80–0.96)	0.004
Perceived personal relationship	1.04 (1.00–1.08)	0.070	1.08 (1.04–1.13)	<0.001
Health promotion	1.02 (0.96–1.08)	0.531	1.13 (1.06–1.20)	<0.001
Enablement	0.98 (0.96–1.00)	0.076	0.98 (0.96–1.00)	0.038
Severity of baseline unwell group of symptoms	1.28 (1.22–1.34)	<0.001	1.20 (1.13–1.26)	<0.001
Severity of baseline frequency group of symptoms	1.33 (1.25–1.40)	<0.001	1.28 (1.20–1.37)	<0.001
Medical problems	1.04 (0.99–1.08)	0.089	1.06 (1.01–1.11)	0.010
Urinary frequency (times per day)	1.02 (1.01–1.03)	0.003	1.01 (1.00–1.02)	0.049

^a The sensitivity groups are compared with the sensitive group given antibiotics. Other variables assessed were urinary frequency (number of times per day), nocturia frequency, age leaving full-time education, marital status, the number of medical problems, perception of doctor communication (a communication and partnership approach, health promotion, interest in the effect on life), Somatic Symptom Inventory and health anxiety (Whitley Index).

antibiotics, antibiotic resistance and other key variables in determining such outcomes. The findings suggest that there is a role for doctors to be enabling and positive about the natural history and provide useful information about which variables predict natural history (a past history, somatic symptoms, the severity of baseline symptoms) and the likely major role of both antibiotics and antibiotic resistance.

Potential study limitations

- Measurement bias. We assumed that symptoms had settled at the last point rated by patients, which provides a conservative estimate of symptom duration and the impact of antibiotics and antibiotic resistance.
- Type I error (chance). Type I error is a little unlikely for the main findings as these are highly statistically significant and the pattern is similar for both symptom duration and the severity of frequency symptoms.
- Type II error (power). The study had complete results for 500 patients and so had reasonable power.
- Confounding. We have controlled for a large range of patient and doctor confounders that have not been assessed in previous studies and have demonstrated that there are likely to be important confounders of such natural history data (a 10–30% change in estimates). By comparing the impact of management with an antibiotic to which infection is resistant and no offer of antibiotics, which would be expected to be similar, we have also helped clarify what outcomes are more likely to be truly associated with antibiotic resistance.
- Selection bias. Selection bias was probably not a major factor as a high percentage of women invited to join the study took part (less than 5% of women declined to participate). Although 18% did not provide information about symptom resolution, loss to follow-up was not related to key baseline variables and so a significant response bias is unlikely.

TABLE 15 Association of antibiotic resistance and other variables with the 'frequency' group of symptoms at days 2–4

Sensitivity^a	Univariate analysis			Multivariate analysis		
	Severity (0 = no problem; 6 = as bad as it could be), mean (SD)	Mean difference compared with sensitive group (95% CI)	p-value	Severity (0 = no problem; 6 = as bad as it could be), mean (SD)	Difference compared with sensitive group, beta- coefficients (95% CI)	p-value
Sensitive (<i>n</i> = 224)	1.52 (1.04)			1.474 (0.88)		
Unknown (<i>n</i> = 47)	1.69 (0.98)	0.16 (-0.32 to 0.46)	0.342	1.65 (0.88)	0.18 (-0.11 to 0.47)	0.229
Resistant (<i>n</i> = 40)	2.11 (1.16)	0.58 (0.22–0.95)	0.002	2.01 (0.89)	0.54 (0.22–0.87)	< 0.001
No antibiotics (<i>n</i> = 17)	1.54 (1.23)	0.02 (-0.51 to 0.56)	0.938	2.07 (0.90)	0.60 (0.14–1.05)	0.011
Urethral syndrome (<i>n</i> = 183)	1.70 (1.12)	0.18 (-0.03 to 0.39)	0.092	1.83 (0.88)	0.36 (0.17–0.56)	< 0.001
Beta-coefficients						
Positive approach to the natural history	-0.04 (-0.14 to 0.06)	0.417		-0.18 (-0.28 to -0.08)		0.001
Perceived personal relationship	0.06 (0.01–0.11)	0.030		0.10 (0.05–0.15)		< 0.001
Somatic Symptom Inventory	0.07 (0.04–0.09)	< 0.001		0.03 (0.001–0.05)		0.017
Past cystitis	0.27 (0.05–0.48)	0.016		0.19 (0.00–0.37)		0.047
Severity of baseline unwell group of symptoms	0.22 (0.17–0.28)	< 0.001		0.08 (0.02–0.14)		0.014
Severity of baseline frequency group of symptoms	0.39 (0.33–0.44)	< 0.001		0.40 (0.33–0.46)		< 0.001

a As in previous tables, the sensitivity groups are compared with the sensitive group given antibiotics. If the complete data available for univariate analysis are used, the estimates are:

sensitive 1.82 (1.37); resistant 2.37 (1.38); no antibiotic 1.99 (1.40); urethral syndrome 1.95 (1.37).

TABLE 16 Association of antibiotic resistance and other variables with 'unwell' group of symptoms at days 2–4

Sensitivity ^a	Univariate analysis			Multivariate analysis		
	Severity (0 = no problem; 6 = as bad as it could be), mean (SD)	Mean difference compared with sensitive group (95% CI)	P-value	Severity (0 = no problem; 6 = as bad as it could be), mean (SD)	Difference compared with sensitive group (95% CI)	p-value
Sensitive (n = 224)	0.97 (1.06)			1.02 (0.85)		
Unknown (n = 47)	1.43 (1.24)	0.46 (0.09–0.84)	0.015	1.34 (0.86)	0.32 (0.02–0.61)	0.036
Resistant (n = 40)	1.43 (1.21)	0.46 (0.06–0.86)	0.024	1.36 (0.87)	0.34 (0.01–0.66)	0.041
No antibiotics (n = 17)	0.92 (1.06)	-0.06 (-0.64 to 0.53)	0.853	1.25 (0.88)	0.22 (-0.26; 0.71)	0.366
Urethral syndrome (n = 183)	1.28 (1.30)	0.31 (0.08–0.54)	0.009	1.28 (0.86)	0.26 (0.07–0.45)	0.009
Beta-coefficients						
Enablement		-0.02 (-0.04 to 0.01)	0.253		-0.03 (-0.05 to -0.01)	0.004
Perceived personal relationship		0.05 (0.00–0.11)	0.065		0.05 (0.00–0.09)	0.032
Somatic Symptom Inventory		0.10 (0.07–0.12)	< 0.001		0.04 (0.02–0.06)	0.001
Severity of baseline 'unwell' group of symptoms		0.53 (0.48–0.58)	< 0.001		0.48 (0.42–0.54)	< 0.001

a As in previous tables, the sensitivity groups are compared with the sensitive group given antibiotics. If the complete data available for univariate analysis are used, the estimates are:
sensitive 1.18 (1.36); resistant 1.55 (1.37); no antibiotics 1.62 (1.37); urethral syndrome 1.47 (1.37).

- Generalisability. Because of the mixed locations of the GP practices, in both rural and urban settings, and the range of demographics in the women, these results should be generalisable within the UK.

Main results: natural history of urinary tract infections

Urinary frequency was the most common symptom rated as a moderately bad problem and also the symptom that on average lasted longest; many women also felt significantly unwell and had restricted activities. The group of patients not given antibiotics and those with antibiotic-resistant organisms complained of moderately severe symptoms lasting 5 days, with most individual symptoms being rated moderately bad or worse for on average 4–5 days after seeing the doctor or nurse. Patients with sensitive organisms or those with unknown resistance (most of whom would be expected to have sensitive organisms)³⁶ had a 50–60% shorter duration of symptoms rated a moderately bad problem, and these differences persisted when controlling for other confounding variables. Although the duration of more severe symptoms and the severity of symptoms have not been reported previously in prospective studies, our findings are consistent with previous observations of the association of antibiotic resistance with prolonged more minor symptoms.^{35,36} The pattern of results (i.e. the similarity of symptom duration and severity for those with no antibiotics and antibiotic resistance), the persistence of the effects when controlling for confounding and the size of the effects suggest that both antibiotics and antibiotic resistance are associated with clinically important differences in symptom duration for symptoms rated as moderately bad or worse by patients.

We have demonstrated empirically that there are two groups of symptoms (a frequency group and an unwell group). Although antibiotic resistance and also no antibiotics are associated with an increase in the severity of frequency symptoms (dysuria, frequency and nocturia), it is less clear whether antibiotics and antibiotic resistance affect the unwell group of symptoms (abdominal pain, restricted activities and feeling unwell).

Patients with the urethral syndrome had symptoms of similar duration and severity to those with confirmed UTI; previous observations that antibiotics are associated with an improvement in

symptoms for patients who are nitrite and leucocyte negative on dipstick (who have presumed urethral syndrome) may be explained by the poor NPV of nitrite and leucocytes in primary care settings.⁴²

Other predictors of symptom duration

The finding that a positive approach to diagnosis and prognosis is associated with shorter symptom duration independently of other variables, and in a relatively well-defined syndromic presentation, supports previous observations that a positive approach is associated with reduced symptom duration in both observational studies and trials^{39,43} and reinforces the likely importance of doctors providing positive information about the natural history. The finding that a perceived personal relationship is associated with prolonged symptoms is probably due to reverse causality, as this patient group is more likely to have had previous prolonged and serious illness or frequent attendance and hence to have altered symptom perception. Patients reporting frequent somatic symptoms are often well known to doctors and are likely to attend more frequently;³⁷ the current study also suggests that they are likely to suffer or report more prolonged symptoms. The current findings also suggest that patients with a past history of cystitis and more severe baseline symptoms could also be advised that symptoms may take a little longer to settle. Such women – i.e. those with numerous somatic symptoms and severe baseline symptoms, particularly if they have a past history of cystitis – are arguably a priority group for prescribing antibiotics.

Conclusion

At presentation to their GP the majority of women in the study suffered from multiple symptoms rated as a moderately bad problem or worse and half felt unwell and had a significant restriction in daily activities. Doctors should probably remain positive about the natural history for patients with suspected UTI. Patients with a past history and those with frequent somatic symptoms and severe baseline symptoms can be given a realistic indication that more severe symptoms may last longer than the average 3 days. Antibiotic resistance or not providing antibiotics is associated with a 50–60% longer duration of more severe symptoms and more severe frequency symptoms in the days immediately after presentation.

Chapter 4

A randomised controlled trial of dipsticks, symptoms scores and self-help advice in the management of urinary tract infection

Background

Urinary dipsticks are used very widely in primary care and are the most commonly used NPT. The aim of using dipsticks is to try and target treatment to the 60% of women who have UTI whilst minimising antibiotic use for women who do not have UTI. The previous validation studies (see Chapters 1 and 2) have shown that dipsticks and clinical scoring algorithms can potentially help to modestly improve the precision of diagnosis by improving the PPVs;⁴² however, if clinicians are to use dipsticks they need to have strategies to deal with the poor NPVs. We are not aware of any trial that has evaluated dipstick or clinical management algorithms in comparison with the realistic alternatives such as empirical antibiotic treatment, empirical delayed prescribing and prescribing according to MSU results. Previous studies using empirical delayed antibiotics in respiratory infections have resulted in good symptom control, less belief in antibiotics and reduced reconsultations.^{34,38,44}

Objective

The objective of this study was to compare the effectiveness of management using dipstick or clinical algorithms with the effectiveness of alternative management strategies (empirical antibiotic treatment, delayed prescribing and targeted prescribing based on MSU results).

Method

The study was supervised by a trial steering committee that included a patient representative and which was under the chairmanship of Professor David Mant. The study took place in general practices in south-west England. Patients were recruited between June 2003 and May 2005. The target group of patients was non-pregnant women

presenting with a suspected uncomplicated UTI. This group was chosen as it is the group presenting most frequently with suspected UTI in primary care and also the group for whom antibiotic use is not mandatory.

Exclusions

Those for whom antibiotic treatment is more definitely indicated (children, men, pregnant women, patients with pyelonephritis, nausea, vomiting or other severe systemic symptoms) and women aged over 75 (as the relationship of symptoms to bacteriuria is different in this group²⁰); patients with psychotic illnesses or dementia or those needing terminal care were also excluded as they might be unable to accurately fill in the diary.

Data collection

Patients with suspected UTI were recruited by the clinician (GP or practice nurse) on presentation. The clinician documented patients' baseline symptoms, clinical information and demographic details (age, sex and postcode), and noted whether antibiotics were prescribed. The patient kept a daily record of symptoms, grading severity – 0 (no symptoms), 1 (a very slight problem), 2 (a slight problem), 3 (a moderately bad problem), 4 (a bad problem), 5 (a very bad problem) or 6 (as bad as it could be). The symptoms (dysuria, haematuria, frequency during day and night, 'smelly urine', 'tummy pain', generally feeling unwell and restriction of daily activities) were based on the common presenting symptoms of UTI¹⁸ and these were presented in a diary format, which has previously been validated and shown to be sensitive to change for other acute infections.²⁶ To help improve completeness of the diary, patients were also phoned by the research assistant after 3 days to check that there were no problems with the diary. No questions were ever asked about compliance or a return to the surgery as this could have altered

patient behaviour. Patients were asked to return their diaries to the surgery in a Freepost envelope on completion.

Notes review

Notes were reviewed blind to study group by a research assistant to document MSU use, antibiotic prescription and referrals.

Laboratory analysis

MSU samples were transported and analysed, as described in Chapter 1.

Randomisation

Patients were randomised within the consultation to one of five management groups: empirical antibiotic treatment (immediate antibiotics); empirical delayed antibiotics (patients were asked to wait 48 hours but could use antibiotics at their discretion); antibiotic targeted by symptom score (two or more of urine cloudy, urine offensive smell, moderately severe dysuria or nocturia); antibiotics targeted by dipstick algorithm (nitrites or leucocytes and a trace of blood); or antibiotics targeted by MSU results (symptomatic treatment until MSU results available) (*Figure 1* and see Appendix 3 for more details). Randomisation

using random number tables was in blocks to balance group numbers. Once consented, patients were allocated to a management group by the opening of a sealed opaque numbered envelope containing the instruction sheets for one of the five management groups. Sealed envelopes were used to facilitate randomisation and the implementation of this complex study – to ensure that only the sheets that the clinician needed were there. The potential to undermine randomisation was minimised by careful attention to maximising equipoise when presenting the study to clinicians, and by emphasising that women in all groups had access to antibiotics at their request. Sequential envelope use was also audited during the study to ensure integrity of randomisation.

Secondary interventions

As normal management is to use immediate antibiotics, we judged that it was necessary to control self-help advice in other groups to avoid a major imbalance of self-help advice. To control the advice given, and also to provide secondary information about the utility of such advice, a number of secondary interventions were randomised across the above groups in a factorial design: a patient information leaflet containing tips on self-help; advice to use over-the-counter (OTC) herbal remedies; advice to use bicarbonate;

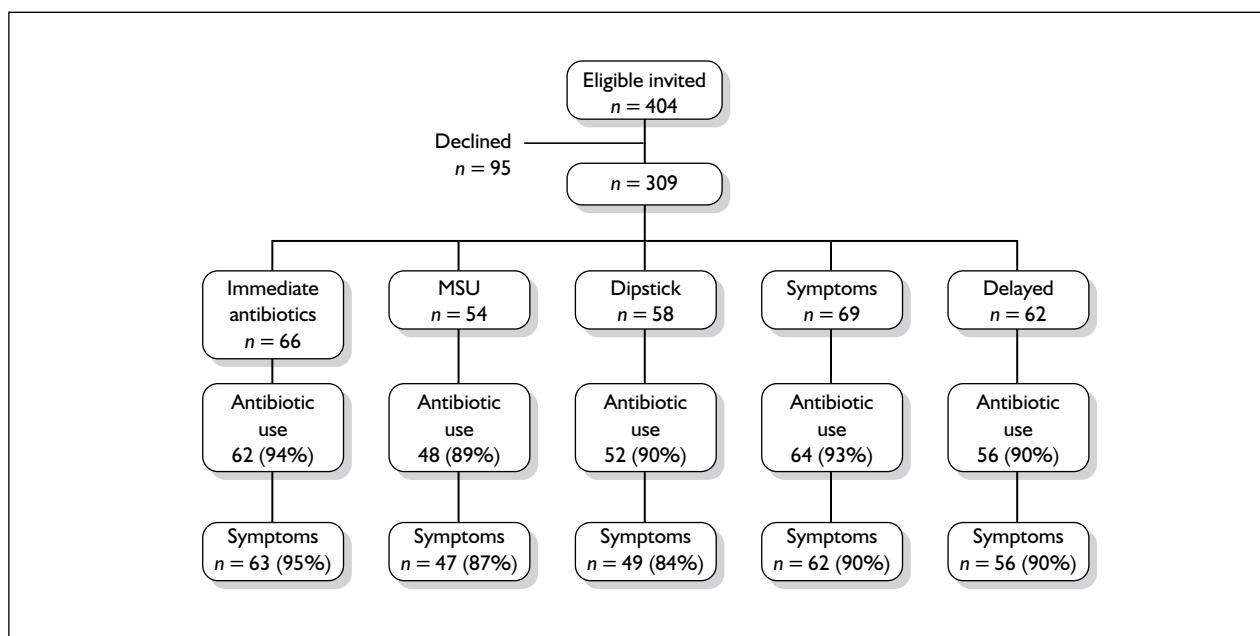


FIGURE 1 CONSORT flow chart. Numbers and percentages randomised to five basic groups, and documentation of antibiotic use and symptom duration. Eligible invited based on clinician report.

advice to use orange juice and cranberry juice), (see Appendix 4). These secondary interventions were not part of the original protocol but were agreed with the NCCHTA before commencing the trial.

The use of advice sheets

For each patient a structured advice sheet was used, supporting the initial management according to the proposed strategy and as used successfully in previous studies from this group.^{33,34,45–47} This was a pragmatic study and as such allowed variation according to negotiation with patients, as would happen in practice.³⁴ Thus, although clinicians negotiated initial antibiotic management based on the sheets, they were allowed to negotiate providing immediate antibiotics when there were strong patient expectations. Conversely, as long as the initial proposed management was the management indicated by the sheet, doctors and nurses had discretion to document dipstick results and order MSUs, negotiated either because of patient pressure/expectation or because of clinical perceptions of the requirement for adequate documentation of diagnosis. Health professionals were asked to document what they did in each case and we used this information in the analysis to assess whether the results were confounded by such behaviour. We performed an in-depth review of 38 case notes with the health professionals concerned in the largest recruiting practice regarding the reasons why MSUs and dipsticks were used when not indicated by the advice sheets.

Sample size (alpha = 0.05; beta = 0.2; nQuery Advisor sample size programme for multiple groups)

Based on previous consensus decisions,⁴⁶ a small difference in symptoms was judged to be if, on average, one in two patients rated one symptom as a slight problem rather than a moderate problem. Based on the means and standard deviations from the pilot study, assuming that the MSU and delayed groups had diary scores 0.5 points higher than the other groups required 260 patients, allowing for up to 20% loss to follow-up. This sample size was agreed with the NCCHTA after the start of the first phase but before the trial commenced, once pilot data were available.

Analysis

We assessed the impact of the management strategies using multiple regression, mutually

controlling for all interventions. We used negative binomial regression for duration of symptoms (because of overdispersion of the data), multiple linear regression for the severity of symptoms, logistic regression for antibiotic use and repeat consultations, and Cox regression for time to first reconsultation. Our primary assessment was of the overall significance of each intervention factor, using the LR test for factors when there were multiple levels (e.g. five basic groups) and *t*-tests otherwise. We report the estimates of differences compared with the control group for each factor with the 95% CIs (i.e. in the case of the antibiotic management factor, the control group was immediate antibiotics, and for the other factors the control groups were no leaflet, no advice to use fruit juice and no advice to use bicarbonate). In a previous observational cohort, the exploratory factor analysis of the severity of symptoms demonstrated two groups of symptoms: these were increased day frequency, increased night frequency and urgency and dysuria (a ‘frequency’ group of symptoms; Cronbach’s alpha 0.77); and abdominal pain, restricted activities and feeling unwell (‘unwell’ group of symptoms; Cronbach’s alpha 0.80); therefore we analysed these two sets of symptoms separately.

Results

As might be expected with the randomisation method, numbers between groups differed, but there was no evidence of subversion of randomisation – there was no alteration in the order of envelope use and there were no significant differences by management group for the key baseline variables of severity of symptoms reported before seeing the doctor, the number of somatic symptoms reported⁴⁸ and past cystitis (all of which were important confounders of outcome in previous studies) (*Table 17*). For the self-help advice groups there were some differences between groups (*Table 18*) but either these did not predict outcome (education, medical problems) or when outcome was predicted by the variable (particularly somatic symptoms – the Somatic Symptom Inventory) the estimates of outcomes in randomised groups were unaffected. We were able to document symptom severity and duration in 277 women (90%).

There were differences between groups in the number of patients for whom clinicians reported sending an MSU to the laboratory at the index consultation [immediate antibiotics 23% (15/66), MSU 89% (48/54), dipstick 36% (21/58), symptom score 33% (23/69), delayed antibiotics 15% (9/62);

TABLE 17 Baseline comparison of five main groups [mean (standard deviation) unless specified]

	Immediate antibiotics	MSU	Dipstick	Symptom	Delayed antibiotics	p-value
Frequency symptoms ^a	3.52 (1.25)	3.57 (1.52)	3.26 (1.30)	3.52 (1.25)	3.78 (1.22)	0.504
Unwell symptoms ^a	2.67 (1.30)	2.39 (1.26)	2.58 (1.41)	2.76 (1.53)	2.69 (1.34)	0.790
Married, n (%)	27/39 (69)	25/38 (66)	34/42 (81)	37/49 (76)	27/39 (69)	0.558
Age left education (years)	17.9 (2.3)	17.0 (2.4)	17.8 (2.8)	17.5 (2.6)	17.5 (2.5)	0.603
Number of somatic symptoms (SSI) ^b	3 (1–8)	4 (1–6)	4 (2–6)	3 (2–6)	4 (2–8)	0.886
Number of medical problems ^c	2 (1–8)	2 (1–6)	2 (1–6)	3 (1–6)	2.5 (1–8)	0.550
Previous cystitis, n (%)	40/46 (87)	35/41 (85)	32/39 (82)	43/50 (86)	35/41 (85)	0.978

^a 0 = no problem; 6 = as bad as it could be.
^b Somatic Symptom Inventory [median (interquartile range)]. We used a version modified for self report.⁴⁹ Patients indicated the number of medically unexplained symptoms severe enough to interfere with normal life or that required seeing a doctor.
^c Number of medical problems [median (interquartile range)]: a list of major medical problems (e.g. back pain, diabetes, arthritis, etc., free space for listing other) were documented by patients and the number listed counted.

$\chi^2 = 81, p < 0.001$]. There were also differences between groups in the number of patients for whom dipstick results were documented [immediate antibiotics 50% (33/66), MSU 52% (28/54), dipstick 95% (55/58), symptom score 55% (38/69), delayed antibiotics 29% (18/62); $\chi^2 = 55, p < 0.001$]. Whether or not a doctor sent an MSU or documented dipstick results at the first consultation did not alter the effect of randomisation group on any outcome (i.e. including these variables in the models did not alter the estimates). The review and discussion of cases in which dipstick documentation and MSUs ordered were not prompted by the advice sheets (for 38 consecutive patients) made it clear that initial management had probably not been subverted. The main reasons highlighted were patient expectation; professional perceptions about the need for adequate documentation (dipsticks being regarded as 'useful' even if management was not based on them); and occasionally clinical reasons (e.g. a higher risk of complications was expected; a more definite initial diagnosis was required).

Use of antibiotics

In total, 66% (36/54) of the MSU group had confirmed UTI. There were significant differences in the number of women who waited at least 48 hours before taking antibiotics [immediate antibiotics 8% (5/60), MSU 43% (20/47), dipstick 30% (15/50), symptom score 19% (11/58), delayed

antibiotics 53% (28/53); $\chi^2 = 34, p < 0.001$]. There were also differences in the number taking antibiotics [immediate antibiotics 97% (58/60), MSU 81% (8/47), dipstick 80% (40/50), symptom score 90% (52/58), delayed antibiotics 77% (41/53); $\chi^2 = 11.7, p = 0.02$]. Women had very similar beliefs in the effectiveness of antibiotics [immediate antibiotics 72% (44/61), MSU 74% (43/46), dipstick 79% (37/47), symptom score 73% (41/56), delayed antibiotics 72% (36/50)].

Symptoms

The average duration of symptoms rated moderately bad or worse in the immediate antibiotics group was 3.5 days. Overall, there were no significant differences in symptom duration, severity of frequency symptoms or severity of unwell symptoms between the antibiotic management strategies (Table 19, LR test). The upper limits for the 95% CIs suggest that it is very unlikely that any of the alternative strategies would result in poor control of the frequency group of symptoms (the main outcome). However, those who delayed antibiotics for 48 hours or more were likely to suffer a 37% longer duration of symptoms rated moderately bad (IRR 1.37, 95% CI 1.11–1.68, $p < 0.001$). The impact of delaying more than 48 hours predominantly applied to the MSU group (LR test for interaction for five groups $p = 0.08$; LR test for MSU group versus other groups $p = 0.02$) (Table 20). The MSU group delayed longer (the

TABLE 18 Baseline comparison of self-help advice groups [mean (standard deviation) unless specified]

	No leaflet	Leaflet	No bicarbonate	Bicarbonate	No herbal	Herbal	No juice	Orange juice	Cranberry juice
Frequency symptoms ^a	3.60 (1.35)	3.45 (1.26)	3.56 (1.40)	3.50 (1.22)	3.52 (1.37)	3.53 (1.24)	3.54 (1.38)	3.59 (1.22)	3.45 (1.31)
Unwell symptoms ^a	2.65 (1.40)	2.61 (1.35)	2.67 (1.37)	2.59 (1.38)	2.71 (1.349)	2.54 (1.23)	2.42 (1.30)	2.77 (1.43)	2.73 (1.38)
Married, n (%)	74/101 (73)	76/106 (72)	71/99 (72)	79/108 (73)	79/105 (75)	71/102 (70)	57/74 (77)	47/66 (71)	46/67 (69)
Age left education (years)	17.6 (2.61)	17.5 (2.43)	17.7 (2.66)	17.4 (2.39)	17.2 (2.32)	18.0 (2.66)	17.6 (2.59)	17.4 (2.49)	17.6 (2.51)
Number of somatic symptoms (SSI) ^b	3 (1-6)	4 (2-8)	3 (1-7)	4 (2-6)	4 (2-7)	3 (1-6)	3 (1-6)	4 (2-6)	3.5 (1-8)
Number of medical problems ^c	2 (1-6)	2 (1-8)	2.5 (1-7)	2 (1-7)	2 (1-7)	2 (1-6)	2 (1-6)	2 (1-6)	3 (2-8)
Previous cystitis, n (%)	92/109 (84)	93/108 (86)	93/110 (85)	92/107 (86)	93/100 (85)	92/107 (86)	74/82 (90)	60/72 (83)	51/63 (81)

a 0 = no problem; 6 = as bad as it could be.

b Somatic Symptom Inventory [median (interquartile range)]. We used a version modified for self report.⁴⁹ Patients indicated the number of medically unexplained symptoms severe enough to interfere with normal life or that required seeing a doctor.

c Number of medical problems [median (interquartile range)]: a list of major medical problems (e.g. back pain, diabetes, arthritis, etc., free space for listing other) were documented by patients and the number listed counted.

TABLE 19 Impact of the different management strategies on symptoms, antibiotic use and reconsultation

	Duration of moderately bad symptoms (days), negative binomial IRR	Frequency symptom severity, ^a mean difference (95% CI)	p-value	Unwell symptom severity, ^a mean difference (95% CI)	p-value	Use of antibiotics, n (%) or OR (95% CI)	Time to reconsultation, HR (95% CI)	p-value
Immediate antibiotics	Mean 3.54 (SD 2.63); IRR set to 1.00	Mean 2.20 (SD 1.19)		Mean 1.63 (SD 1.33)		58/60 (97)	HR set to 1	
MSU	1.21 (0.92–1.61)	0.173	-0.07 (-0.53 to 0.39)	0.768	0.05 (-0.44 to 0.55)	0.828	0.15 (0.03–0.73)	0.019
Dipstick	0.91 (0.68–1.22)	0.533	-0.48 (-0.94 to -0.02)	0.040	-0.28 (-0.77 to 0.20)	0.254	0.13 (0.03–0.63)	0.011
Symptom score	1.11 (0.85–1.44)	0.454	-0.41 (-0.84 to 0.02)	0.061	-0.35 (-0.80 to 0.11)	0.136	0.29 (0.06–1.55)	0.149
Delayed antibiotics	1.12 (0.85–1.47)	0.411	-0.11 (-0.56 to 0.33)	0.618	-0.18 (-0.65 to 0.30)	0.461	0.12 (0.03–0.59)	0.009
LR test		0.369		0.132		0.392		0.345
Leaflet	1.06 (0.89–1.27)	0.515	-0.29 (-0.58 to 0.01)	0.056	-0.08 (-0.39 to 0.23)	0.596	0.74 (0.36–1.53)	0.011
Herbal	0.92 (0.77–1.10)	0.380	-0.31 (-0.60 to -0.01)	0.040	-0.47 (-0.78 to -0.16)	0.003	0.63 (0.30–1.30)	0.417
Orange juice	1.13 (0.91–1.41)	0.265	-0.32 (-0.67 to 0.04)	0.081	-0.26 (-0.64 to 0.11)	0.172	0.43 (0.19–1.00)	1.08 (0.77–1.53)
Cranberry juice	1.18 (1.95–1.47)	0.129	-0.01 (-0.37 to 0.34)	0.944	0.02 (-0.36 to 0.39)	0.933	1.27 (0.47–3.43)	0.051
Bicarbonate	0.89 (0.74–1.06)	0.185	-0.16 (-0.45 to 0.13)	0.292	-0.18 (-0.49 to 0.13)	0.242	1.21 (0.60–2.47)	0.69

^a 0 = no problem; 6 = as bad as it could be.

All estimates in the table are adjusted for all other interventions in the table. When differences are quoted these are the estimated differences compared with the control for that group (all of the basic antibiotic management groups are compared with the immediate antibiotics group; leaflet is compared with no leaflet; orange juice and cranberry juice are compared with water; Uvacin is compared with no Uvacin). Thus, taking the first row the MSU group has an IRR of 1.21 compared with the immediate antibiotics group and frequency symptom severity was 0.07 lower and unwell symptom severity was 0.05 higher than for those in the immediate antibiotics group; taking the last row, advice to use bicarbonate resulted in an 11% shorter duration of symptoms (IRR 0.89) and the frequency symptom severity was 0.16 lower and the unwell symptom severity was 0.18 lower than for those not given advice to take bicarbonate.

TABLE 20 Estimates of symptom duration for women who delayed taking antibiotics by 48 hours or more

	Duration of moderately bad symptoms (days), negative binomial IRR	Net effect of delaying in each group ^a
Immediate antibiotics	IRR set to 1.00	
MSU	0.82	1.73
Dipstick	0.84	1.19
Symptom score	1.13	0.96
Delayed antibiotics	1.06	1.21
Took on day 3 or later	1.54	
Interaction terms		
Took on day 3 or later MSU	1.37	
Took on day 3 or later dipstick	0.92	
Took on day 3 or later symptom score	0.55	
Took on day 3 or later delayed antibiotics	0.74	

a Net effect = effect in group \times effect of taking after 3 days \times interaction term for that group.

average day starting antibiotics for the immediate antibiotics, MSU, dipstick, symptom score and delayed antibiotics groups was 1.19 days, 2.18 days, 1.43 days, 1.40 days; and 2.21 days respectively), but this does not explain why the delayed group did not also suffer worse symptoms as the delay in starting antibiotics was similar in this group.

A secondary finding was that advice to use a herbal treatment (bearberry extract) resulted in significantly less severe frequency and unwell symptoms, but few patients reported using the named and most common commercially available extract (Uvacin). Advice to use bicarbonate and cranberry juice had little effect on any of the outcomes and there was a borderline effect of leaflets for frequency symptoms.

Effect of self-help advice on reported behaviour

Providing advice modestly altered reported behaviour: 57/75 (76%) of those advised to take cranberry juice reported taking cranberry juice [versus 43/88 (49%) who reported using cranberry juice when advised to use water alone, or 40/78 (51%) who reported taking cranberry when advised about orange juice]. Similarly, 49/78 (63%) of those advised to use orange juice did so compared with 19/88 (22%) of those advised to use water and 21/75 (28%) advised to use cranberry juice. A total of 36% (45/124) of those advised to use bicarbonate did so versus 11/117 (9%) of those not advised to

and 14% (17/123) of those advised to use a herbal extract did so versus 1% (1/118) of those not advised to.

Use of resources

There was little difference between groups for recontact recorded in the notes in the 4 weeks following consent [immediate antibiotics 6/58 (10%), MSU 9/52 (17%), dipstick 6/51 (12%), symptom score 8/64 (13%), delayed antibiotics 5/58 (9%); $p = 0.79$] nor for use of MSUs [immediate antibiotics 3/58 (5%), MSU 3/52 (6%), dipstick 4/51 (8%), symptom score 5/64 (8%), delayed antibiotics 3/58 (5%); $p = 0.95$]. The average follow-up time was 575 days (range 35–968 days). There was no overall difference in time to reconsultation, but as we hypothesised a priori⁶ there was suggestive evidence that reconsultations might be reduced in the delayed antibiotics group (see Table 19).

Patients who waited for 48 hours before using their prescription reconsulted less (hazard ratio 0.57, 95% CI 0.36–0.89, $p = 0.014$). Because some data for the Cox regression was missing (for time to first reconsultation), we also used more complete data to assess whether reconsultation had occurred, controlling for time between randomisation and notes review. In the immediate antibiotics group, 32/58 (55%) returned whereas other groups reconsulted less [MSU OR 0.65, 95% CI 0.30–1.40, $p = 0.273$; dipstick OR 0.87, 95% CI 0.40–1.90, $p = 0.727$; symptom score OR 0.57 95% CI 0.27–

1.18, $p = 0.129$; delayed antibiotics OR 0.44, 95% CI 0.21–0.95, $p = 0.036$].

Discussion

This study is one of the few to document prospectively the outcomes of different initial management strategies of antibiotic use for suspected UTI.

Potential study limitations

- Measurement bias. For a very small minority of patients who did not complete the diaries that were sent back, our results will provide a conservative estimate of symptom duration and the impact of the different management strategies.
- Type I error (chance). Type I error is possible, as for the main strategies there were five groups. We hypothesised worse symptomatic outcomes in the MSU and delayed antibiotics groups compared with the symptom score or dipstick groups in the days after seeing the doctor *a priori*, and this pattern was apparent for the MSU group for those patients who waited more than 48 hours before taking antibiotics; however, as the overall LR test was not significant these results must be interpreted with caution.
- Type II error (power). The study had complete results in 277 (90%) patients and so had more power than originally calculated; however, we cannot exclude small effects of the management strategies on symptoms in individual groups.
- Confounding. There was no evidence from auditing the use of envelopes or from the baseline tables that randomisation was subverted. When differences between groups were found, which are likely to be chance findings, the potential for confounding was assessed; however, no evidence was found.
- Generalisability. The reasonable response to invitation, the mixed locations of the general practices in both rural and urban settings and the range of demographics in the women should make these results generalisable; in addition, the presentation and incidence of confirmed UTI in this sample were almost identical to those seen in the previous observational studies.
- Group differentiation. There was group differentiation in dipstick use, MSU ordering and the willingness of women to delay using

antibiotics. Our detailed review of cases suggested that clinicians are likely to want to carry out an MSU or to document dipstick results in a substantial minority of patients, irrespective of initial antibiotic policy. This is sometimes because of patient expectation (which might be expected to change over time as doctor behaviour changes⁴⁴), sometimes for legitimate clinical reasons (e.g. uncertainty about the development of complications) and occasionally because of an overly optimistic view of the accuracy of dipsticks (e.g. wanting 'adequate documentation', which may be misguided given the poor NPVs of dipsticks⁴²). Estimates were altered little when these behaviours (i.e. MSU/dipstick) were included in the model, which suggests little confounding by such behaviours.

Main results

Use of antibiotics, belief in antibiotics and reconsultation

As 66% of the MSU group had confirmed UTI – similar to the previous study⁴² – our optimal target to lessen antibiotic use was realistically 34%. We achieved a modest reduction in antibiotic use (20–25%) in all groups except for the symptom score group. Although these reductions are probably useful for public health,⁸ and the effect might plausibly increase with time as patient expectations change,⁴⁴ the magnitude of the effect is nevertheless in contrast to the results of delayed antibiotic prescription among patients with respiratory infections in which patients mostly do not use their antibiotics.^{34,46} The difference seen with respiratory infections is perhaps not surprising given that the minority of respiratory infections are bacterial whereas the majority of suspected UTIs are. There was suggestive evidence that delayed prescribing might reduce reconsultation and although this was of borderline significance – probably because of the relatively low power of this analysis – this was what had been hypothesised *a priori* based on previous evidence.⁴⁴ Those women who did wait for 48 hours were also likely to reconsult less.

Mid-stream specimen of urine use

There was no evidence that either using MSU as an initial strategy to guide antibiotic prescribing or the use of MSUs by doctors as part of their overall clinical management made any difference to MSU ordering in subsequent consultations. As with antibiotic prescribing, it is likely that as perceptions change among both patients and doctors regarding

the need for MSUs in clinical management of uncomplicated infections, laboratory resource use from such unnecessary investigation could be significantly reduced.

Symptom control

Although there was no clear evidence that on average symptom control was much worse in any of the groups, there was some evidence that on average if women waited more than 48 hours than they had poorer symptom control, particularly for the MSU group. This may be a chance finding but it may be that women find it more difficult/distressing to have to wait for a laboratory result (in effect being disempowered regarding their symptoms) rather than being given the freedom to choose when to stop the delay (the empirical delayed antibiotics group). The finding of worse symptoms in patients who delay for too long is in agreement with evidence from observational studies and trials²⁸ that antibiotics and antibiotic resistance make a difference of about 2 days for moderately bad symptoms (see Chapter 3). The evidence was suggestive that dipsticks or symptom score may reduce symptom severity. Although this could possibly be due to better targeting of antibiotics combined with avoidance of the side effects of antibiotics (e.g. thrush), there was

no direct evidence of this, and some caution is required as the overall LR test for the difference of symptom severity between groups was not significant.

Self-help advice

There was evidence that patients did change behaviour in response to advice but the effect was modest (13–41% reported changing behaviour). Advice to drink juices rather than water, advice to use bicarbonate or provision of a leaflet made little impact on symptoms. Although advice to use herbal extracts may possibly help improve symptoms, this result must be viewed with some caution as use of the bearberry extract (which was specifically mentioned) only increased modestly.

Conclusion

Patients who delay by more than 48 hours while waiting for MSU results are likely to have much poorer symptom control. Immediate antibiotics targeted using dipsticks with a delayed prescription as backup or an empirical delayed prescription achieve similar symptom control to empirical antibiotics and help reduce antibiotic use.

Chapter 5

Economic evaluation of the randomised controlled trial

Background

There is very little data available on the cost-effectiveness of different strategies for managing UTI. A previous decision analysis concluded that empirical antibiotic treatment was likely to be the most cost-effective strategy⁷ but this study had no direct evidence from randomised controlled trials on the likely estimates of costs and benefits of different management strategies.

In this chapter we report the results of a cost-effectiveness analysis carried out alongside the clinical trial.

Methods

The initial aim of the economics component of this research was to estimate the resource usage associated with the five strategies in the randomised controlled trial. However, as participants recorded the number of days of moderate/severe symptoms in the trial we were able to perform a cost-effectiveness analysis of cost per day of moderate/severe symptoms avoided. This information was obtained from participants' completed diaries, up to a maximum of 14 days after recruitment.

We estimated costs from an NHS perspective. These comprised the cost of the recruitment visit to the GP, including any MSUs and dipstick tests carried out, and the cost of antibiotic prescribing at this visit. As it is possible for the care received in the recruitment visit to have 'knock-on' effects on subsequent use of services for UTIs, we also estimated the cost of care in a follow-up period. The follow-up periods used were the month and the year following recruitment into the study. As far as it was possible to identify, all costs measured were related only to the treatment of UTIs. All costs were estimated for the year 2005/6 and were in UK pounds sterling.

For the recruitment visit we obtained data from participating GPs. This included data on the length of time taken for the consultation. The time

taken was costed using unit cost figures published by the Personal Social Services Research Unit (PSSRU) at the University of Canterbury.⁵⁰ In total, 39/309 cases had missing data for length of time taken for consultation. These data were imputed using a regression method with study group as an explanatory variable (SPSS version 14). This was checked against the original data to ensure that the means and standard errors of the estimated time in consultation for the imputed variables were equivalent to those of the original variable (means were within 1% in all cases). The costs of MSU and dipstick tests in the randomised trial were based on whether the GP or laboratory reported an MSU or whether a dipstick was carried out. The cost of the MSU was assumed to be the laboratory cost plus any consumables used. These were obtained from the finance department of the local NHS Trust. The time taken to perform the test would have been calculated as part of the time taken in the recruitment visit and so would already have been costed. Data were available on whether the study participant had antibiotics dispensed after the recruitment consultation. Again, considerable data were missing for this variable (41/309 cases), and so these missing data were imputed using the methods described above. For costing purposes we assumed that antibiotics were prescribed according to protocol, i.e. trimethoprim. For this, a cost was obtained from the *British National Formulary*.⁵¹

For the follow-up period, data were obtained directly from GP notes. Two periods of follow-up were used in the costing study: 1 month and 1 year after recruitment. Longer periods of follow-up were available from the data but it was not felt that the strategy employed at the recruitment visit would have had an effect that persisted for more than 1 year. All consultations with the GP were costed using an estimated cost per visit obtained from the PSSRU unit costs.⁵⁰ This was based on a standard 10-minute consultation. MSUs performed in reconsultations were recorded and these were costed using the methods described earlier. Also recorded were antibiotics used. Finally, data were obtained on referrals to secondary care in the follow-up period. Referrals were excluded if they were unlikely to be attributable to UTIs; this was

carried out in consultation with a clinical expert blind to group (PL). Referrals were included if there was evidence in the case notes that they had in fact taken place and they were costed using NHS reference costs.⁵²

Analysis

The data were analysed using Microsoft Excel and SPSS version 14. CIs were estimated using SPSS. Although there were 309 participants in the study, follow-up resource use data were not available for all. The cost analysis reported here was performed on participants for whom follow-up data were available – this comprised 283 individuals. To test the robustness of estimates obtained from the analysis we also estimated 95% percentiles using 1000 bootstrap samples.^{53,54} This bootstrapping procedure was also used to estimate both cost-effectiveness and cost-effectiveness acceptability curves (CEACs) for the cost per day of moderate/severe symptom avoided. CEACs show the varying probability that an intervention is cost-effective as the value placed upon the outcome of interest is varied.

Results

Table 21 shows the resources used by the participants in the five study groups. For the recruitment visit there appear to be differences in the numbers taking antibiotics by group. There is little variation in resource use between groups at the 1-month follow-up; however, as would be expected, there is more variation at the 1-year follow-up as these events are likely to have a more tenuous relationship with initial randomisation group.

These resource use values were used to estimate the costs of treatment by randomisation group. These values are given in *Table 22*. It can be seen that the total costs for 1 month's follow-up are similar between all five groups. Costs ranged from £30.70 to £37.10. The majority of these costs were attributed to the recruitment consultation, as there were few reconsultations in this period. For total costs for the 1-month follow-up there was a statistically significant difference between the MSU group and the immediate antibiotics, symptom score and delayed antibiotics groups. There were no statistically significant differences between

TABLE 21 Resource use by participants in the five antibiotic management groups

	Immediate antibiotics	MSU	Dipstick	Symptom score	Delayed antibiotics
<i>n</i>	58	52	51	64	58
Recruitment visit to GP – mean time in minutes	11.7	12.6	12.9	11.7	12.4
Recruitment visit – MSU, <i>n</i>	15	46	20	22	8
Recruitment visit – dipstick, <i>n</i>	31	26	48	36	18
Recruitment visit antibiotic prescriptions, <i>n</i> (%)	56 (97)	42 (81)	41 (80)	56 (88)	43 (75)
Reconsultations within 1 month					
GP	6	9	7	9	6
MSU	3	3	4	5	3
Number of antibiotic prescriptions	4	7	6	8	5
Referrals to secondary care	0	0	0	0	0
Reconsultations within 1 year					
GP	46	27	39	43	31
MSU	27	7	17	24	19
Number of antibiotic prescriptions	39	26	37	40	31
Referrals to secondary care	2	0	1	0	0

Excludes 26 cases who did not have complete follow-up data.

TABLE 22 Cost estimates (£) of randomised controlled trial strategies

	Immediate antibiotics	MSU	Dipstick	Symptom score	Delayed antibiotics
Recruitment visit					
GP visit	25.7 (23.5–27.9)	27.8 (24.7–30.8)	28.3 (25.8–30.8)	25.6 (23.1–28.2)	27.2 (24.3–30.1)
MSU	1.1 (0.6–1.6)	3.8 (3.5–4.2)	1.7 (1.1–2.3)	1.5 (1–2)	0.6 (0.2–1)
Dipstick	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.4 (0.4–0.4)	0.2 (0.2–0.3)	0.1 (0.1–0.2)
Antibiotics	1 (0.9–1)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.8–0.9)	0.7 (0.6–0.8)
Total	28 (25.7–30.4)	32.6 (29.6–35.7)	31.2 (28.6–33.8)	28.2 (25.7–30.8)	28.7 (25.7–31.6)
1-month follow-up					
GP visit	2.3 (0.5–4)	3.8 (1.5–6.1)	3 (0.6–5.4)	3.1 (1–5.2)	2.3 (0.2–4.3)
MSU	0.2 (0–0.5)	0.3 (0–0.5)	0.3 (0–0.7)	0.3 (0.1–0.6)	0.2 (0–0.5)
Secondary care referrals	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Antibiotics	0.2 (0–0.4)	0.4 (0–0.7)	0.3 (0–0.5)	0.3 (0–0.5)	0.1 (0–0.2)
Total	2.7 (0.6–4.8)	4.4 (1.8–7.1)	3.6 (0.8–6.5)	3.7 (1.2–6.2)	2.6 (0.3–5)
1-year follow-up					
GP visit	17.4 (11.2–23.7)	11.8 (6.5–17.2)	16.8 (10.5–23.2)	14.8 (8.7–20.9)	11.8 (6.6–16.9)
MSU	2 (1.1–3)	0.7 (0.2–1.1)	1.4 (0.8–2.1)	1.6 (0.8–2.4)	1.4 (0.6–2.3)
Secondary care referrals	9.4 (−5.9 to 24.7)	0 (0–0)	2 (−1.9 to 6)	0 (0–0)	0 (0–0)
Antibiotics	1 (0.6–1.5)	1 (0.5–1.5)	1.6 (1–2.2)	1.1 (0.6–1.7)	1.2 (0.5–1.9)
Total	29.9 (10.5–49.3)	13.5 (7.5–19.5)	21.9 (11.8–31.9)	17.5 (10.3–24.7)	14.4 (7.9–20.8)
Total cost in first month	30.7 (27.2–34.2)	37.1 (33.1–41)	34.9 (31.3–38.4)	31.9 (28.6–35.3)	31.3 (27.2–35.3)
Total cost in first year	57.9 (37.5–78.3)	46.1 (40.1–52.2)	53.1 (42.7–63.4)	45.8 (38.6–53)	43.1 (35.8–50.3)

For the 1-month follow-up there were significant differences between the MSU group and the immediate antibiotics, symptom score and delayed antibiotics groups.

any of the groups for the 1-year follow-up; these differences were examined using *t*-tests. To test the robustness of these results we also estimated bootstrapped confidence intervals.^{53,54} In all cases these were extremely close to those generated using parametric methods.

We examined effectiveness in terms of the number of days of moderate/severe symptoms and also the cost-effectiveness in terms of the cost per day of symptoms avoided. This was carried out on those cases for which there were completed data for both costs and also symptoms and hence uses a smaller sample than that used for costs. The samples used for the five groups were as follows: immediate antibiotics 56/58, MSU 46/52, dipstick 42/51, symptom score 60/64, delayed antibiotics

54/58. These estimates of cost-effectiveness are presented in *Table 23*. Strategies in this table are ranked by mean cost (for 1-month follow-up). The effectiveness estimates are included as negative values, as number of days of moderate/severe symptoms is a disbenefit, i.e. the less the better. Incremental costs and effects are given compared with the least costly strategy. Most strategies are dominated, which means that there is some other strategy that is both less costly and more effective. The least costly strategy is immediate antibiotics. Compared with this strategy the dipstick strategy generated additional symptom days avoided and a cost of £9.30 per additional symptom day avoided.

The problem with *Table 23* is that it takes no account of uncertainty – one strategy could

be dominated by another if its mean values were slightly worse and there may be no statistically significant differences between the cost or the effectiveness estimates. To allow for this uncertainty we estimated CEACs for the strategies, which are shown in *Figure 2*. These show the probability that a given strategy is cost-effective as the value placed upon the unit of effect is varied. If one strategy is more costly and more effective than another strategy then the higher the value placed upon the unit of effect the more likely that strategy is to be cost-effective. For example, if the value placed upon the unit of effect is zero then the more expensive strategy can never be cost-effective. If a very high value is placed upon the measure of effectiveness then there is an increased chance that the value of the extra benefit produced exceeds the extra cost and hence the strategy will be cost-effective. We varied the value of a day of moderate/severe symptoms avoided from £0 to £100. The strategy most likely to be cost-effective varies with changes in the value of a symptom day avoided. If a symptom day avoided is given a low value, i.e. less than approximately £10, then immediate antibiotics is likely to be the most cost-effective strategy. For values over £10, the dipstick strategy becomes the most likely to be cost-effective. Because of the uncertainty present, we can never be more than approximately 70% certain that the dipstick strategy is the most cost-effective.

Discussion

The results presented here suggest that all strategies have similar resource implications. The MSU strategy was statistically significantly more expensive than the immediate antibiotics strategy only at 1-month follow-up. There were no significant differences at the 1-year follow-up. It may be the case that if the sample sizes were larger there would be more statistically significant differences but the absolute magnitude of these are

likely to be comparatively small. This is expected as the tests used in this study are low cost and routine and would be expected to make only small changes to the amount of time GPs would spend in providing care for UTI. There is therefore likely to be no strong reason to prefer any particular strategy on the basis of costs.

Regarding cost, a uniform length of follow-up was used in the economic evaluation to be able to compare each individual on a like-for-like basis. There were varying lengths of total follow-up time used in this study; this depended on when individuals were recruited, as those recruited early would tend to be followed up for longer. Using a set follow-up time would ensure that any differences in costs were not due to differences in follow-up. The fact that there were no differences in mean costs at the 1-year follow-up suggested that 1 month of follow-up was probably sufficient to detect any differences in costs. For the cost-effectiveness analysis we only present costs for the 1-month follow-up as we only have an outcome measure that covers the 14 days after recruitment.

The cost-effectiveness analysis shown here presents estimates of the cost per symptom day avoided. Extreme caution needs to be exercised here in the interpretation of these results because of the effectiveness data underlying them. For the cost-effectiveness results to be credible requires that the effectiveness results also be credible. Although the dipstick group had slightly better results than the MSU group for symptoms, the question is whether we sensibly rely on this data? The data for improvement in moderately severe symptoms were not significant. Supporting a probable improvement in the dipstick group is the fact that the severity of symptoms was also less in the dipstick group. Is it plausible that the dipstick group would have better results than the immediate antibiotics group? This is a little difficult to understand as the immediate antibiotics

TABLE 23 Cost-effectiveness of the different strategies

	Cost	Effects	Incremental costs	Incremental effects	Incremental cost-effectiveness
Immediate antibiotics	£31	-3.6			
Delayed antibiotics	£32	-3.9	Dominated		
Symptom score	£32	-3.9	Dominated		
Dipstick	£35	-3.1	£4.60	0.5	£9.30
MSU	£37	-4.2	Dominated		

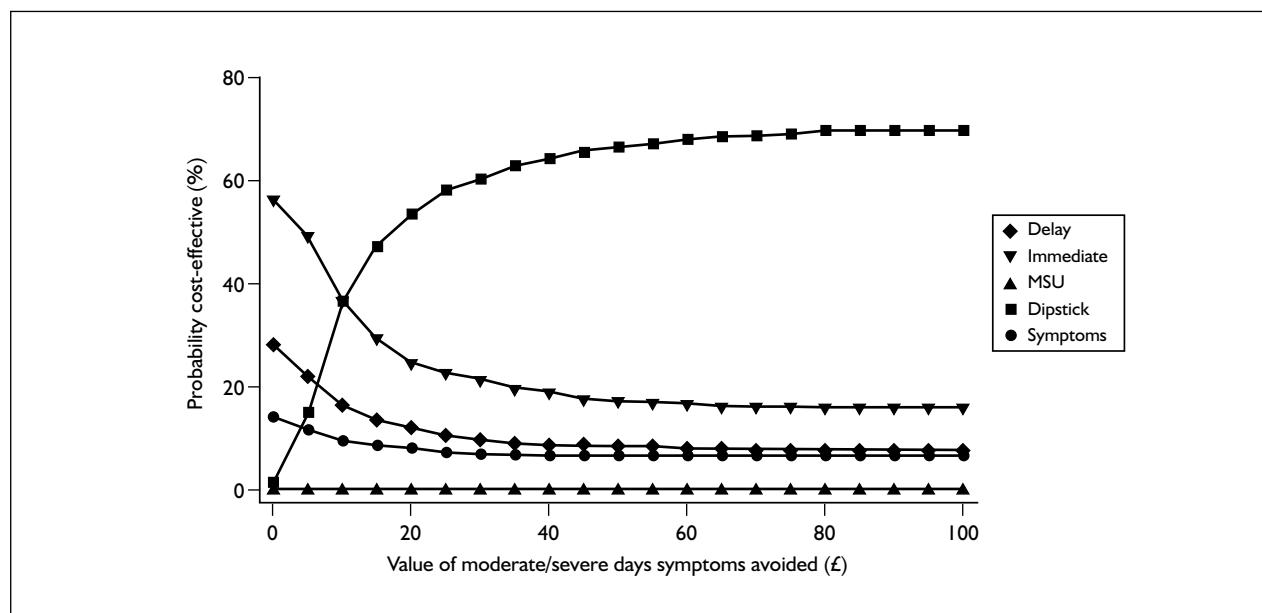


FIGURE 2 Cost-effectiveness acceptability curve for 1-month follow-up.

group should be giving all those with infection antibiotic cover, whereas the dipstick group will only imperfectly target such people. Perhaps the possible improvement in the dipstick group should not be dismissed too lightly – it is possible that patients' symptom management is helped by the security of feeling that they know from dipsticks whether or not they have an infection.

The effectiveness measure used in this analysis is cost per day of moderate/severe symptom avoided. This presents a problem of interpretation as it requires an understanding of the value of a symptom day avoided and how much the NHS should be prepared to spend to achieve this. Our analysis suggests that symptom days can be avoided at an approximate cost of £10 per symptom day. A judgement would therefore need to be made on whether the value of avoiding days of moderate/severe symptoms would exceed this.

It should be noted that some potentially important factors are not included in this analysis. We take no account of productivity factors, i.e. avoiding

symptom days may mean that individuals need less time off work. This would mean that the interventions may be more cost-effective than indicated here as avoiding symptoms would also incur less costs in terms of lost productivity. In addition, the current analysis does not attempt to quantify any benefits associated with reducing the use of antibiotics. This is a potentially important omission and would mean that interventions that were able to reduce the use of antibiotics would be undervalued in this framework.⁵⁵ The current analysis supports in principle previous work suggesting that performing an initial MSU in all patients is not likely to be cost-effective in clinical practice.⁵⁵

Conclusion

Dipsticks are likely to be cost-effective if the value of saving a day of moderately bad symptoms is valued at £10 or more, but caution is required given the considerable uncertainty surrounding the estimates.

Chapter 6

Qualitative interview study: urinary tract infection and its management

Introduction

Urinary tract infections are common conditions in primary care with one out of two women suffering at least one episode in their lifetime.^{1,29} There is debate about the self-limiting nature of UTIs and the value of antibiotic medication.²⁸ For respiratory infections it is clear that the issue of patient expectation for antibiotic medication shapes prescribing behaviour for many but not all doctors;^{56,57} however, the research evidence provides mixed messages about the level of patient expectation for antibiotic medication. Recent evidence suggests that doctors may in fact overestimate patients' expectations for medication;^{58,59} however, little is known about women's experiences of UTI and their views on taking antibiotic medication.

Understanding patients' experiences, their journey to the doctors, why they seek medical help and their expectations when they seek such help is important. As Calnan⁶⁰ explains, 'patients' specific reasons (and experiences) will have an influence on the way they evaluate the care that they receive'. More broadly, as Zola⁶¹ highlighted over 30 years ago: 'The very labelling and definition of a bodily state as a symptom as well as the decision to do something about it is in itself part of a social process' and understanding this process is critical to our understanding 'the treatment and control of illness'.

This chapter describes a qualitative interview study, nested in our larger randomised controlled trial. Interviews explored patients' views on UTI and the acceptability, or otherwise, of being asked to wait to take antibiotic medication. Information gathered contributes to our broader goal of building a coherent framework of understanding about UTI and its best management. These qualitative data help to indicate how future service interventions, such as the use of backup antibiotic strategies, may be organised to meet the needs of the consumers of such services.

Methods

Participants and procedure

To be eligible for inclusion participants had to fulfil three criteria:

- be participants in the larger trial and have consented to participate in a single face-to-face interview
- be eligible to delay antibiotics as part of the initial strategy in the trial (see Appendix 3)
- live within a 40-mile radius of the university department.

The second criterion ensured that we were able to explore participants' thoughts on the appropriate treatment of UTI and their views on the acceptability or otherwise of being asked to delay taking antibiotic medication. The third criterion was introduced as a practical measure to limit the amount of travel required by the interviewers.

In 2006, GL and ST conducted the interviews in women's homes. Each interview lasted an average of 1 hour and was audio taped and transcribed verbatim. A professional freelance scribe and GL transcribed the tapes. GL and ST made field notes and kept a 'journal' in which impressions of the interviews, the interview process and key points were noted. Later, during analysis, these reflexive notes provided a useful reminder of broader contextual and process features of the research, such as how interviewees had responded to particular questions.

The interviews

A semistructured topic guide ensured that critical topics were covered in each interview whilst also providing the necessary flexibility to allow participants to raise issues that were germane to them. The interviews were designed to elicit participants' understanding of and attitudes towards UTI and its management. Key domains covered were (see Appendix 3 for the topic guide):

- experiences of UTI and health-seeking behaviour
- perspectives on and understanding of UTI and its treatment.

The main outcome measures were patient experiences of UTI, beliefs regarding treatment and views about the management strategy of 'backup' or delayed antibiotic prescribing.

Analysis

Drawing on the principles of analytic induction, thematic analysis was an iterative process.⁶² Manual coding was used throughout and this began with initial familiarisation with the data. Vertical and horizontal familiarisation initially involved annotating transcripts with 'a priori' codes, based on the original research aims and topics covered by the interview guide. Next, summary cards were made for each interview on which we 'extracted' and 'summarised' key annotations/codes, our overall impressions and some verbatim quotations.⁶³ This ordering of data facilitated the later identification of emerging issues raised by participants and recurrent patterns, and permitted comparisons with concepts present in the literature.

Following initial coding, further reading and rereading of the transcripts dictated slight modifications to the thematic framework to manage contradictions and nuances in the data. Following the comparative method, which involves seeking out 'deviant cases',⁶² we aimed to ensure that all observations could be properly accounted for and that key themes were not prematurely formed. We tested the integrity of our observations by performing 'crude counts' of key observations to test their frequency.⁶² Throughout the chapter we draw on a selection of exemplary fragments from the 20 transcripts to illustrate key themes. Saturation of themes had occurred in the 20 interviews.

Representation of thematic analysis can result in the decontextualisation of speakers' words, which may fragment or misrepresent the intended meaning as they appeared in the original sequential narrative. Therefore, care was taken to analyse the participants' words in the broader context of the surrounding utterances (vertical analysis) to ensure a fair interpretation of the meaning of the fragments reproduced in this chapter.

Results

In total, 33 women were approached to take part in the interview study: 27 agreed and 21 were interviewed (we had reached saturation). Reasons for refusal included only being available in the late evening, when the researchers were not available, and being too busy at work. Following one tape failure we produced 20 audio recordings. As is routine in qualitative work, the sample size was never intended to permit comparisons of attitudes and understandings according to participants' face-sheet characteristics, such as age, occupation and so forth, although we did anticipate that there might be some differences between women with a previous history of UTI and those without.

Seven women were in the symptom score group, nine in the empirical delayed antibiotics group and two each in the symptom score and MSU groups. The characteristics of the women participating in the qualitative study were similar to those of the overall trial cohort: 65% versus 73% married, 88% versus 85% past cystitis, mean 3.00 versus 2.6 number of medical problems, 17.6 versus 17.6 age leaving education, mean 3.5 versus 3.5 severity of frequency symptoms at baseline respectively.

The findings are divided into two broad parts:

- part one: experiences of UTI and health-seeking behaviour
- part two: perspectives on and understanding of UTI and its treatment.

Included within each of these two broad parts are several subsidiary themes. Part one illuminates the different stages in participants' prediagnostic illness trajectory – from first noticing symptoms to going to see the doctor. Part two moves on to participants' reported beliefs about UTI, including their views on the use of a backup antibiotic management strategy.

Part one

Experiences of urinary tract infection and health-seeking behaviour

All interviews opened with the question, 'Could you just start at the beginning and take me through the first signs that something was different?' This opening question solicited participants' stories in which they described:

- symptom onset and recognition
- action taken in light of their symptoms

- pivotal triggers that led to their consulting behaviour.

In this first section we describe these three stages. All three sections provide an insight into the journey that participants take to the doctor and the huge amount of work that participants undertake on the 'path from person to patient'.⁶¹

Symptom onset and recognition

First, let us establish the symptoms that were recurrently reported and the process of symptom recognition when participants were faced with bodily change.

Symptoms

When women were invited to describe the beginning of their illness episode they volunteered a list of diverse signs and symptoms (see also Maltuerud and Baerheim⁶⁴). All interviewees reported experiencing multiple signs and symptoms concurrently. The quotations below exemplify the range of concurrent bodily and emotional changes described:

It was just really uncomfortable and I was in pain quite a lot and I couldn't, you know, just get on with my normal day to day things ... like going to work [emphasis added].

Interview 12

[It was] incredibly painful to go to the toilet ... and I was getting backache and ... I was getting really irritable ... It was uncomfortable to sit down and ... it was really smelly ... it was affecting how I was feeling generally, like emotionally and physically [emphasis added].

Interview 14

These exemplary quotations illustrate how women introduced their illness episode. They rarely relayed a single symptom, but multiple bodily changes were volunteered together with the impact of such change, both physical and emotional (*Table 28* in Appendix 5 provides an indication of the symptoms described when interviewees first experienced their bodies as 'non-normal').

Women's accounts of their symptoms resonated with Zola's⁶¹ differentiation of two ways of 'communicating about one's bodily complaints'. Drawing on interviews with patients recruited in a general hospital waiting room she reported one type of description that 'seemed to reflect a rather specific organic dysfunctioning ... [e.g.

discharge ...] while the second type represented a more global malfunctioning (aches and pains, energy level etc.)'. Nearly half of the women with suspected UTI reported that the symptoms impacted in a generalised or global way, affecting their mood and general overall healthiness. Women oscillated back and forth between 'organic' and 'global' descriptions and in so doing they conveyed the symptoms and the implications of their symptoms in general terms.

Symptom recognition: how women 'locate' their symptoms

Once women had identified their core symptoms they repeatedly proceeded to talk about their reaction to and assessment of their symptoms. Whilst doing so, the majority (15 out of 20) drew on their previous experiences of a UTI to 'locate' their symptoms and to help them to ascertain what the symptoms might mean. In short, a previous experience provided an established frame of reference, which aided their efforts to make sense of their bodily changes:

Well, first of all, I was in pain going to the toilet and I'd had cystitis, years ago ... and I knew what the signs were.

Interview 18

I just thought, oh, that hurt at bit, going to the loo, and I thought I hope it's not cystitis.

Interview 11

From the sensation I knew what it was likely to be.

Interview 6

The study by Everitt *et al.*⁶⁵ on the management of conjunctivitis found a similar drawing on past experience to help understand symptoms and anticipate the likely impact of the symptoms: 'Because I had suffered a few episodes of cystitis before I knew it was likely to be a problem' (interview 6).

However, not all of those with previous episodes reported being able to interpret the symptoms straightforwardly. Although the symptoms seemed familiar, labelling them or deducing a diagnosis could be a difficult process:

I used to permanently have cystitis ... and then the last year I've been getting two or three uncomfortable episodes ... I couldn't tell at that time, the symptoms, whether it was sort of thrush or cystitis.

Interview 5

Indeed, a few of the women reported using thrush remedies instead of cystitis remedies in the first instance.

For the five women in the interview group who had no previous history of a UTI the process of symptom recognition was more difficult. Generally, participants in this smaller group spoke of not being able to recognise the bodily changes – ‘I didn’t know what was wrong, I never used to suffer’ (interview 4; waited for 10 days to seek help) – or being able to deduce a probable diagnosis – ‘I thought ... maybe I might be having the change’ (interview 19; waited for 3 weeks to seek help).

Of course, women drew on knowledge gleaned from other peoples’ experiences and general knowledge and so the absence of a previous episode did not preclude a best hunch diagnosis. No previous experience, however, could exacerbate uncertainty and heighten concern about the validity of a best hunch diagnosis.

Let us now consider the actions that women reported taking in light of their symptoms.

Taking action

Following the initial symptom experiences, once women were aware of the physical changes and had made some assessment of those changes, they ‘assumed the sick role’ in and through their adoption of a number of familiar illness management strategies (see Suchman’s⁶⁶ stages of illness model; note that these strategies or stages are not mutually exclusive):

- lay referral networks (family, friends and chemists)
- lay remedies: OTC/other self-care measures
- ‘wait and see’: defer decision and observe symptoms.

Lay referral networks

The first strategy is a well-known ‘stage’ in many conditions on a journey to diagnosis in most patients’ illness paths, although this was the least discussed strategy (e.g. Zola,⁶¹ Calnan,⁶⁰ Suchman⁶⁶). When explicitly asked about ‘lay consulting’, participants’ reports suggested that such networks for UTI were of fairly limited value. This was likely to have been influenced by the high number of participants with previous experience of a UTI. These participants seemed well placed to deduce a probable diagnosis without seeking validation or advice from members of their lay network.

Over and above family and friends the most common first step for advice involved a visit to the chemist (interviews 1, 8, 11 and 18). Three of the four who discussed such a visit described being advised to visit the doctor – their seeking help was directly ‘sanctioned’ and the chemists took ‘responsibility for the decision to seek aid’.⁶¹ Just thinking for one moment about ‘reattendance’, on one occasion such advice followed a participants’ index consultation in which they were reportedly advised to try an OTC and hold off having antibiotics:

[The doctor] said do a sample for her and go and try some over-the-counter ... methods I went to the pharmacy and they said ‘how bad is it?’ and I said, ‘my back is starting to hurt and I’m passing blood’ ... she said, ‘well it’s gone way past the counter stage, you need to, sort of, get some antibiotics’.

Interview 11

Similarly, interviewee 1 reported her visit to the chemist to purchase Cystes and described how the chemist advised her to consult a doctor because of the severity of her described symptoms; she did not purchase or use the product and later consulted her doctor.

Patients’ decision-making takes place in a wider sociocultural context⁶¹ and their decisions to seek help were inevitably shaped by other factors. Before seeking formal medical help the majority of participants discussed the use of lay remedies.

Lay remedies and self-care

In total, 11 of the 20 interviewees spoke specifically and voluntarily about consuming more fluid before their consultations (interviews 5–7, 9–15 and 19; interviewee 4 had interstitial cystitis and we did not discuss self-medication):

I drank gallons and gallons of water ... normally at first indication it’s straight to the lemon barley and loads and loads of water and a hot water bottle and normally it shifts.

Interview 10

I just drink lots and lots of fluids and drink cranberry juice, I use a lot of cranberry, and reduce my caffeine intake.

Interview 14

I had been drinking a lot of water and just trying to flush my system out as much as possible ... and I went straight to the supermarket and got myself some cranberry

juice ... we tend to have a fruit smoothie every day so I got cranberry juice and just made a smoothie with that ... I don't drink tea or coffee.

Interview 15

As well as the specific 'healthful' activity of drinking water and cranberry juice, participants regularly volunteered giving up or cutting down their caffeine intake. Five of the interviewees (2, 8, 16, 17 and 18) reported using an OTC product such as Cystes before consulting. OTC products were most often used in combination with drinking extra fluid:

Prior to [my GP visit], I had taken, done the usual thing, drink plenty of fluid, that didn't work, so I'd been into the chemist and bought one of the over-the-counter remedies.

Interview 16

I think I'd tried to ... do it myself, you know, by doing the bicarb of soda ... drinking lots and ... I'd used the Cystes as well.

Interview 17

The remaining three interviewees varied from the majority. Unlike the other participants they did not attempt to convey a strategy of self-management. Interviewee 3 said that she wanted to treat it quickly before it worsened and hence did not have the time to self-treat; interviewee 5 described how her 'sachets were out of date' and hence she could not self-treat; and interviewee 20 did not volunteer a method of self-treatment. When asked what she would normally do she replied, 'I'm not very good at drinking, I've got to be honest I don't drink the recommended quota'. (We return to the moral accounting work embedded in much of the interviewees' talk a little later.)

It is noteworthy that in their stories participants volunteered their use of OTC products and frequently spoke of their increased intake of fluids once they had detected the first signs or symptoms of UTI. This high level of self-care corresponds with other studies, which show that patients can and do self-care before consulting. Indeed, as Nettleton⁶⁷ points out, 'most health care work is carried out by lay people either in the form of self-care or caring for relatives and friends'. We are all, as she reminds us, 'health workers'.

'Wait and see': deferring a decision and observing symptoms

The majority of women reported waiting for a period and deferring their decision to seek help

(see Suchman⁶⁶). Participants' reasons for their 'wait and see' policy and the duration of their waits varied. In terms of the duration waited, seven of the 20 reported waiting for under 4 days, five for a week, one interviewee specified a 10-day wait and, finally, three waited for between 3 and 4 weeks before seeking medical help (see Table 29 in Appendix 5 for the exact number of days reportedly waited by each participant before seeking help).

For those who waited the longest period there was a sense that their symptoms had not impacted on their lives to a degree that merited seeking help. For example, interviewee 2, who waited for 3 weeks, spoke about being 'symptomatic' for that period but that it was not 'horrendous'. Others spoke about external pressures acting as a barrier to seeking help, such as being too busy and finding it difficult to take time out of work: 'I'm a bit busy (slight laughter) ... biding my time' (interview 19). Although being busy could shape a decision to hold off seeking help, it did not preclude self-care:

Right, I'd had cystitis for ... probably a week by the time I went to the doctor ... but I'd been very busy at work and normally just drink lots and lots of fluids and drink cranberry ... I use a lot of cranberry ... but it wasn't making any difference at all.

Interview 14

The great majority explained that they had elected to see if their lay remedies would eliminate their symptoms before going to the doctor. Participants spoke in detail about their self-care activities and the wait to see if their attempts would work:

It started on the Tuesday so I took the sachets for 3 days. Normally ... after a day of the sachets it's normally cleared up ... but this time it wasn't ... so after 3 days I went to the doctor.

Interview 8

Making contact with a medical care provider was the least common first step in a participant's illness journey. Participants' orientation to the use of lay remedies or simply increasing fluid intake suggested a high level of belief in the self-limiting nature of UTIs.

Some reports suggested that the 'wait and see' policy could present somewhat of a double bind. On the one hand participants oriented to a wish to self-care whilst on the other hand they spoke of a need to ameliorate symptoms out of respect for their bodies and the roles they must fulfil

(also implying that antibiotics might speed up the recovery time).

Interviewee 7 had waited for 1 week and had tried to drink cranberry juice and water. Although she had waited for this period she reported the difficulties of waiting and knowing how long a 'reasonable' wait might be:

You're always a bit worried about leaving it for too long because it can be very uncomfortable ... I tend to leave most things for a week or two ... and if it was still there I would go and see the doctor ... it depends how long you can put up with something like that, doesn't it?

Interview 7

Also, implicit in participants' accounts was a further double bind – how to balance their own individual need to seek advice/get reassurance/get medication with a concern to not needlessly 'bother' the doctor. Eventually, certain triggers led all participants to the doctor.

Triggers for help seeking

Four key triggers were evident in participants' reports of their experiences of UTI and their approaches to help seeking. These were:

- the failure to alleviate symptoms through lay remedies
- symptom duration and escalation
- the disruption to normal functioning and the fulfillment of social roles
- concern that it might be a serious illness or become serious.

In many respects each of the four triggers was strongly interconnected. For example, the failure to alleviate symptoms often meant that those symptoms lasted longer than previously experienced and escalated. Similarly, escalating symptoms sometimes led to a degree of disruption to normal routines and such disruption could lead to the inability to fulfill everyday roles. Equally, concern that lasting and/or severe symptoms might indicate something more serious or become (even) more serious pervaded many of the participants' accounts of their path from 'person to patient'.

In this section we deal with each trigger separately to allow a clear exploration of each. Also, to deal with them separately avoids implying that all participants experienced the interconnections noted above. That is, symptoms lasting longer than normal did not necessarily lead to symptom escalation and so forth.

Failure to alleviate symptoms through lay remedies

It should already be evident that when asked to describe what led them to visit their GP the majority of participants first described (in detail) their attempts to self-care before seeking medical help (see Lay remedies and self-care). Failure to alleviate symptoms was by far the commonest trigger for finally seeking medical help (interviews 2, 7–12, 16 and 18):

I tried self-medication, which didn't work.

Interview 10

I started drinking cranberry juice and I drink a lot of water at work anyway, but it just didn't get any better So I decided to go to the doctor.

Interview 9

Prior to [the GP visit], I had taken, done the usual thing, drink plenty of fluid, that didn't work, so I'd been into the chemist and bought one of the over-the-counter remedies. That didn't work, so that's when I went to the doctor in the end.

Interview 16

As an aside, throughout the interviews, when describing their pathways to the doctor, participants went to great narrative lengths to portray themselves as responsible consumers of national health services. For example, in the following exemplary fragment the interviewee's language works to show her as having acted reasonably when faced with illness:

I just drink *lots* and *lots* of fluids and drink cranberry juice ... but it wasn't making any difference *at all* ... so I went to the doctor.

I think I must have gone through ... there was *at least* 3 days where *all I drank* was cranberry juice and it made *no* difference ... *never been* [to doctors for a UTI] before but I just thought at this point *enough is enough* [emphasis added].

Interview 14

Participants' use of language repeatedly invoked a highly responsible rhetoric. In this particular example the participant does not drink just fluid but 'lots and lots of fluid'. Drinking lots did not just fail to make a difference but made no difference 'at all' and so on. Her report that she had never visited a doctor for the UTI also works to convey a minimal user of services. Eventually, her decision to go to the doctor is announced in this highly

'reasonable' narrative context and her seeking help is rendered as a very logical next step in her illness journey.

Returning to participants' 'failed' attempts to self-care, sometimes the corollary of this was the eventual escalation and/or simple 'dragging on' of symptoms. Symptom duration and escalation provided two further triggers for leaving lay remedies behind and moving to the next stage of seeking formal medical help.

Symptom duration or escalation

The majority of interviewees talked about the persistent nature of their index episode and the gradual escalation of their symptoms. Some described their decision to seek medical help as a result of the episode being qualitatively different from previous experiences.

Most of the participants noted the escalation of symptoms: 'It started mild, then got worse so that's why I went to the doctor' (interview 18); 'It was just not going away' and it was 'incredibly painful' (interview 14).

With patterned regularity, while they described their experiences, those with a previous history seemed to use that history to help characterise the nature of their most recent index episode:

This time was different.

Interview 12

I woke up with really bad stabbing pains in my back, um, and it just felt different ... so I went to the doctor. *It didn't feel the same* [emphasis added].

Interview 8

Relative to previous episodes, the index episodes were sometimes experienced as out of the ordinary or 'not normal' in terms of their duration: 'I've had it a couple of times before and it's gone within a couple of days, but this was just dragging on' (interview 12). And sometimes, in terms of severity: 'I've had them before but never as bad as [this one]' (interview 14).

Some explicitly mentioned their concerns that the escalation of symptoms may indicate something more serious that might require medical attention. Thus, in such circumstances, participants' reports oriented to help seeking as the most reasonable course of action:

It wasn't getting better it was getting steadily

worse and I thought well I want to nip this, because you never know really, I had a pain in my back as well ... and I wasn't sure if it was y'know kidneys ... so I thought I better go then.

Interview 5

Although there was a sense that participants reported seeking medical help when they just could not tolerate the pain any longer, the situation was far more complex than a single question of 'pain'.⁶¹ The interruption to everyday life provided a powerful argument for seeking help: 'It just got worse and worse and it got to the stage where I couldn't go to work and I was just in agony' (interview 11) (second visit following delayed prescription).

Indeed, it was common for participants to invoke a classic Parsonian⁶⁸ rhetoric when accounting for their seeking help. That is, they not only sought a speedy recovery but also sought to enable the fulfilment of their social roles.

Disruption to normal functioning and the fulfillment of social roles

Following Zola's⁶¹ work on pathways to the doctor, it was clear that participants did not appeal to symptoms alone as a driver for help seeking. Rather, interviewees' perceptions of the implications of the symptoms led them to seek help. One such implication was a 'perceived interference with vocational or physical activity'.

Expressions of interruption to normal functioning varied, but all were offered as important factors in the decision to consult a medical professional. Some of the participants referred to their childcare duties:

I started drinking cranberry juice and I drink a lot of water at work anyway but it just didn't get any better and having children I didn't want to feel any more poorly than I was feeling So I decided to go to the doctor.

Interview 9

Most, however, appealed to a reason that is 'straight out of the Protestant Ethic', also noted by Zola,⁶¹ or to a duty to stay well in order to fulfill their roles in the community; 'It was making it difficult to work, um, and I was teaching classes as well' (interview 8).

Despite the use of Cystes and increasing her fluid intake, interviewee 18's symptoms did not subside

and also began to disrupt her work: 'It didn't really go and it got worse and I took the afternoon off work, which is unlike me'. Following a second consultation and commencement of a second antibiotic prescription, this particular interviewee reported how she was finally unable to fulfil her employee role: 'I was off work for a whole week actually, which is very unlike me. I was sick and everything, it was horrible' (interview 18).

It is worth noting the accounting work embedded in these fragments. That is, taking time off work is conveyed as extreme and uncharacteristic behaviour. This particular interviewee's narrative turn works to imply that only severe symptoms would lead to such absenteeism and hence her identity as someone who works hard remains intact, as does her identity as a 'reasonable' user of health services.

Work responsibilities and the failure to fulfil them was one of the strongest reasons for seeking help (interview 3):

If I'm at work and I need to carry on then I'm more likely to go to the doctor's than if I've got a few days off and I can ride it out and try and manage things ... not the sort of [job] where you can just ... clear off.

Interview 17

Just one interviewee noted that her symptoms, especially the frequent need to void, hampered her leisure activities as well as her work:

Going to the gym was difficult because I'd always be needing the loo and at work I was just up and down constantly and I couldn't really sit still for a long time because it just got painful and I had headaches ... so I suppose I must have had a bad case.

Interview 14

Participants who described the implications of their symptoms on a 'generalised level' note also: 'I was just to the point, you know, it, it stops life doesn't it ... it stops normal living and that's when I went' (interview 17).

The 'debilitating' implications of symptoms were described as eventually creating a 'breaking point' – 'enough was enough' – and the trigger for help seeking was activated:

It sort of became more and more debilitating and it was realising how debilitating it could be

... the effects of having it became ... quite big ... it was affecting how I was feeling generally, like emotionally and physically ... I just thought at this point enough is enough.

Interview 14

As well as the interference with 'vocational and recreational activities', participants' help seeking seemed to be triggered by concern that the implications of the symptoms might be greater than their best hunch or lay diagnoses might suggest.

Concern that it might be a serious illness or become serious

Finally, regardless of whether participants had had a previous episode or not, the final core driver for help seeking resided in a fear that the symptoms experienced may indicate something more serious or may develop into a more serious condition.

Based on previous experiences, one interviewee stated that her fear of worsening symptoms had led to her help seeking in a preventative fashion. When asked by the interviewer whether her symptoms were severe, she responded: 'Well I was trying to catch them before they got too severe (exhaling/laughter) funny enough!' (interview 7).

This form of 'early' preventative consulting was rare. For others, a generalised 'feeling' that 'all was not well' triggered help seeking. For some, such a feeling was a result of previous experience:

Normally if it's going to shift, it'll shift quite quickly, you know, you get some sort of feeling that it's going to be moving on and you're going to be OK. But this time I didn't so I thought, you know, I'm going to the doctor.

Interview 10

Others spoke in more general terms: 'I just thought, no, this isn't right' (interview 14).

One interviewee stated that the recurring nature of her symptoms led her to worry about her health or her 'system' in general and consequentially she sought reassurance:

I had [an infection] back in February ... and I just got concerned that there may be something fundamentally wrong with my system that needed to be looked at and he just told me there wasn't really anything I need to worry about.

Interview 15

Another interviewee stated that: 'I think I said to the doctor at the time, y'know it wasn't horrendous it was just niggling and I just knew it wasn't right' (interview 2).

In place of preventive help seeking or help seeking based on a general feeling that 'all was not well', some sought medical help in reaction to already severe and frightening symptoms. One expressed a fear about cancer in particular (interview 1), whereas another spoke in general terms about the fear caused by the severity of the pain: '[I was in] terrible pain and [it was] frightening' (interview 8).

In addition to 'pain' as a trigger, 'passing blood and everything' (interview 11) was one of the commonest cited causes for concern. 'Blood' seemed to be one of the strongest triggers:

Actually I did have blood in my urine which made me go to the doctor's cause I ... yeah, I got a bit worried about that, certainly cause of my age.

Interview 19

There was a lot of blood in my water and, um, I got a really big fright with that and that is what prompted me to go and see the doctor ... I just went, ohhhh, there's got to be something wrong here.

Interview 15

I'd had some bleeding as well, so I – I felt that it was a little more of a problem than could just be treated with – with fluids basically, so there was concern for that.

Interview 6

Finally, a fear that the symptoms might develop into something worse also appeared to act as a catalyst for action: 'I'm always aware that it could spread to my kidneys and I could end up having kidney infections and feeling really desperate. So I decided to go to the doctor' (interview 9).

Often, whilst voicing their fears that the symptoms could have developed into something more serious, participants referred to the particular potential for the 'infection' to 'go to the kidneys': 'What if it has gone to the kidneys?' (interview 1).

Of course, sometimes participants' fears were confirmed. Interviewee 8 described how, following her index consultation in which she was asked to delay, she was 'sent home from work'. In her

second consultation she was informed that she had 'more of a kidney infection' and she was prescribed antibiotics. She later spoke of her fear of long-term damage as a result of her episode: 'Since then ... if I do get dehydrated I get a kidney pain. So I'm assuming I've done a little bit of damage that maybe can't be sorted' (interview 8).

Finally, in contrast to the fear that something worse may be indicated by the symptoms experienced, two interviewees focused specifically on their need for medication, and this perceived need provided their rationale for seeking help.

In Part two, participants' expectations for and views about antibiotics are explored, together with their views on the use of a 'backup' management strategy.

Part two: patient views about urinary tract infection and its management

In the second half of the interview participants were asked to move on from their experiences prior to their index consultation to reflect on their thoughts and attitudes about:

- antibiotic medication
- the management strategy of antibiotic delay
- the causes of UTI.

In this chapter we take each of these topics in turn and describe participants' reported thoughts and attitudes about each.

Antibiotic medication

Participants reported a range of attitudes towards, and experiences of, antibiotic medication. In line with findings from earlier work with patients with conjunctivitis,⁶⁵ the majority of participants indicated that they would rather avoid taking antibiotic medication. Just a few indicated strong reasons for their use. Let us take each position in turn.

Antibiotic medication: reasons against

Participants' reasons for wishing to avoid antibiotics varied. Many reported that antibiotics were a last resort, only to be taken when the severity of the symptoms necessitated their use:

I don't really like taking antibiotics unless I'm, you know, unless I think I'm dying [laughter] ... I wouldn't take antibiotics for [UTI] unless it was really, really, really bad.

Interview 14

Overall, such caution seemed to be motivated by three beliefs: in side effects, weakening of the body and natural healing and holism.

Side effects Many of the participants with a previous experience of antibiotics had suffered with thrush (one of the commonest side effects) and this appeared to limit participants' desire for antibiotic medication: 'I know that thrush can be a side effect of the antibiotic and I have suffered that in the past as well, so anything to avoid that situation' (interview 6).

The threat of such effects fuelled a desire to try alternative treatments:

You get thrush or you get constipation, so I'd rather try other methods.

Interview 14

I don't actually want to take antibiotics if I can avoid it ... and the thrush I used to go around in circles with it, with thrush and BV [bacterial vaginosis], which is another similar thing It took me a couple of years to get out of that cycle, so I try to avoid antibiotics as much as I can.

Interview 2

Reticence was also shaped by worry about long-term damage caused by sustained use (e.g. interview 7, used for multiple sclerosis). Concerns about long-term harm were described as shaping decisions about not only whether to take antibiotics but also how to time seeking help:

Well, I know that ... long-term effects, I've been a nurse, I know the long-term effects ... of them and I'd rather not have them if I could, to be honest ... that's why I don't go to the doctor's till it gets really bad.

Interview 20

Others spoke about their allergies to particular types of antibiotics and expressed a consequential need for caution: 'I have to be careful about what ... antibiotics they're giving me' (interview 10). Although some participants appealed to just one core reason to avoid antibiotics, the reasons offered were not mutually exclusive. For example, some had suffered side effects on a previous occasion but also spoke of a desire to protect their body:

Antibiotics in general have caused me a quite severe rash on my legs ... it was just awful ... I

suppose that is one of the reasons but I don't think that's the prime reason. I think the main reason is that I just don't think it is right for the body to keep taking them.

Interview 5

For some, a belief in the attenuating effects of antibiotics and a related desire to protect the body from those effects provided particular motivation for circumspection.

Weakening the body Some explicitly mentioned the weakening effect of antibiotic medication. One participant expressed this as a weakening against other illnesses: 'Taking antibiotics, all it does is weaken you against something else' (interview 14). Another spoke about killing 'good bacteria': 'They just kill all the good bacteria as well as the bad' (interview 2). Just one spoke directly about antibiotic resistance (but when probed was unable to embellish her remark): 'Antibiotic resistance and that sort of thing' (interview 3).

Another spoke about the damaging effects of long-term use and its impact on 'immunity':

I wouldn't like to be someone that takes them a lot cause then they don't work, you know, you just become immune to, you know, it doesn't work, does it, once your system's had an overload of them, you know.

Interview 12

One participant discussed the prolonged nature of the weakening effects of antibiotics whilst one waits for the effect to get 'out of your system':

I just feel that antibiotics kill off everything in the system basically and I feel like it leaves my body defenceless ... for whatever period of time it takes to get it out of the system and I believe it is, it runs into about 6 weeks to actually get antibiotics out of your system after you've been on a course of them I would be left vulnerable if I were to take something for that specific ...

Interview 15

The belief of a weakening effect often coincided with a belief that 'the body heals itself most of the time anyway' (interview 15). For interviewee 5, her motivation to avoid antibiotics was explained with reference to an 'imperative' to care for her body and not rely on 'chemical healing', and a more pragmatic concern to avoid unwanted side effects:

I take antibiotics at the last possible stage; I really don't like taking them. I just don't think they are good for you. I think people pop them too quickly and don't let the body try and you know, deal with its own problems and I do suffer from thrush so I find if I take antibiotics then I think I'll get a recurrence of thrush I prefer a more holistic approach.

Interview 5

In other words, reasons for avoidance were multifaceted, driven in part by a belief in natural health and holism and in part by pragmatic concerns about unwanted side effects.

The strengthening effect of natural healing and holism In contrast to the weakening effects of antibiotics, many participants expressed a belief that it was better and strengthening to embrace 'natural healing':

I don't really like taking antibiotics ... cause I think your body is better if you leave it, not leave it, but if you get it to fight the infections it becomes stronger against them.

Interview 14

Others spoke in more general terms about a preference for natural healing: 'I don't really like taking drugs I have to say. I'd rather deal with things naturally' (interview 2).

One participant talked at length about the need to nurture the body to help with the process of natural healing:

I'm a great believer in the body as a fabulous mechanism and it's got most of its resources to heal itself ... I try to give it as many resources to help it feed itself well I take multivitamins, kind of a mineral vitamin supplement every day, which maybe I don't need to do, but if the body doesn't need it, it will just flush it out I try and look after myself as much as possible.

Interview 15

A belief in the body as its 'own healer' and individual responsibility to help the body to heal led some to discuss their search for alternative treatments:

I'd rather not if there is a way around it, I'd rather not. I'd do ... I look into things at the health food store to see if there's anything that might help.

Interview 1

I do try and combat it myself and sometimes it works and sometimes it doesn't ... so [just in case] always, always would try other things first.

Interview 17

However, as some of the interviewees were probed about what these alternatives might be, it was clearly the case that a great deal of uncertainty existed about what they could use for UTI (interview 16).

I'd rather try other methods, but I'd probably have to go back to the doctor to get the other choices because it is quite difficult, unless you go on the internet to find ... all the information.

Interview 14

It was evident from the majority of interviews that products such as Uvacin, the use of orange juice and even common OTC products were not well known and, when faced with UTI symptoms, increased water and cranberry juice intake was the commonest self-care approach reported. Hence, although participants' narratives indicated support for a conservative approach to antibiotic medication use, in practice they appeared to require advice and information to enable them to close the gap between their stated beliefs and their likely future behaviour (see Everitt *et al.*⁶⁵).

Some participants accounted for the gap between their stated beliefs and their past or future behaviour. For example, interviewee 1 stated a preference for alternative treatments, but despite her searching in health food shops had not found an apposite remedy. She went to quite extraordinary narrative lengths to account for her behaviour:

I haven't to be honest, I haven't – this sounds awful, I haven't had the time, that sounds like I've been a busy bee, but I haven't [found anything as an alternative] ... only the cranberry juice, which is what most sites tell you to drink.

Interview 1

In short, although participants expressed a willingness to try or a strong preference for alternatives to antibiotics, it appeared that a lack of information about what those alternatives might be had thwarted their efforts to avoid antibiotic medication in the past and could do so again in the future.

Antibiotics: reasons for their use

Overall, the few who were persuaded by the utility of antibiotic medication for the management of UTI communicated a more pragmatic approach than their circumspect counterparts. Although two interviewees oriented to the potential problems associated with antibiotic use, their perceived need to resolve symptoms seemed to over-ride any potential problems:

I am sort of aware that, you know [of problems of resistance] . . . I just don't care; I'll give it a try [slight laugh]. . . . If it gets rid of it.

Interview 11

Well I know, obviously, there's a lot of stuff about antibiotics . . . they're being prescribed when they shouldn't be, really . . . and obviously they should only be for infections rather than viruses. Is that right? . . . I mean I'm fine about taking them as long as it sorts out my problem . . . it doesn't bother me.

Interview 18

A pragmatic need to fulfil social roles reportedly shaped participants' initial help-seeking behaviour, and it also seemed to fuel a belief in antibiotic treatment:

I think one is influenced by one's job. If I have to go to a meeting in [place name] I'll go to the doctor and get antibiotics and take them straight away because I've got to be fit.

Interview 3

Implicit in the belief in antibiotics was an assumption that they would result in a faster alleviation of symptoms than would no treatment.

For a couple of participants it was evident that they had not been offered a 'backup' antibiotic but had been prescribed antibiotics for immediate use. Clinical need provided the rationale for using antibiotic medication in these cases. The idea that the symptoms could be self-limiting was not explored and the GP's prescribing behaviour understandably provided further evidence for their use:

I think they're a good thing [slight laughter] . . . I don't know if it would have got better . . . on its own, I don't know. It was just at the stage where antibiotics [were needed].

Interview 11

Another participant appealed to her GP's rational approach to prescribing and hence invoked a scenario in which she could abdicate responsibility or the need to choose:

I haven't come across any GPs that willy nilly give you antibiotics, if you've got a virus, most of them will say, you've got a virus and it will go eventually . . . but in this case he could see I was really suffering and . . . it was not a case of sit back and wait a fortnight, it will go, let's sort it out as soon as we can.

Interview 10

One participant who was offered 'backup' medication discussed how she did not delay and did not use the prescribed Uvacin because 'I knew I needed the antibiotics . . . and they cleared it' (interview 13). Indeed, based on past experience, she was convinced by the necessity of antibiotics and sought help on that basis: 'I went to the doctor because I know damn well that when I get a bout of cystitis, only antibiotics will cure it' (interview 13). However, her certainty of the need for antibiotics was not without its complications, as became clear later in her interview: 'the only answer for me is antibiotics . . . that can't be good, but there again it's a cure, so I don't know' (interview 13).

Participants' reasons for using antibiotics were largely pragmatic and rested on a perceived clinical need, the need to be symptom free and a lack of known alternatives. In the absence of alternatives, participants had taken antibiotics and indicated that they would take them in the future in a similar situation. Most were, however, open to suggestion. For example, being introduced to new remedies, such as Uvacin, was deemed to be a particular benefit of participation in the study overall, and this study experience had opened up potential alternative treatments for the future (e.g. interview 6).

The management strategy of antibiotic delay

It is arguable that the delayed antibiotics group of the trial presented the greatest challenge to doctors if, as some of the literature suggests, patients' demands or expectations for antibiotic medication are high. However, the delay intervention proved to be evaluated relatively positively by 10 of the participants (interviews 2, 3, 5–7, 9, 12, 14, 15 and 20) who were offered the delay option. Just three (interviews 8, 11 and 17) reported negative experiences (the remaining seven participants reported being prescribed antibiotic medication

immediately: interviews 1, 4, 10, 13, 16, 18 and 19). The preponderance of positive reports about the experience of delayed medication corresponded with participants' circumspection about taking antibiotics.

Three of the interviewees reflected on their allocation to the delay arm of the trial in highly positive terms:

She [the nurse] said ... if you agree to take part then you'll have an envelope and you may be given antibiotics, you may not ... and I said well I really would rather not have antibiotics ... but luckily enough, whether she opened it first or not I don't know [laughter], I got the cranberry juice [laughter] one.

Interview 5

I went in and I didn't want to take antibiotics so I was quite glad when he gave me this other [Uvacin] ... but just a bit disappointed it didn't work.

Interview 12

One of the participants reported resolve to avoid antibiotic medication, regardless of her GP's recommendation: 'He didn't give me antibiotics but I wouldn't have taken them anyway ... I'm not a great believer in antibiotics' (interview 15).

This provides one neat indication that consulting behaviour is not necessarily motivated by an expectation for an antibiotic. Interviewee 15 had earlier referred to her 'big fright' when she discovered a lot of blood in her urine. In her case, along with others, it is more likely that seeking help was driven by a need for discussion and reassurance and not, as some might suggest, a perceived need or desire for antibiotic medicine.

Positive experiences

The reasons for positive reports varied. But it was evident that delayed antibiotic medication and being offered 'natural' alternatives were particularly well received by those patients who had indicated a belief in holism and in avoiding orthodox medicine when possible:

I really like the fact that my GP, who I mentally associate with y'know antibiotics and drugs of some sort, has suggested a herbal remedy and fruit juice ... I think it's great ... rather than trying to give me antibiotics straight away I'd love a doctor's practice that really combines all the kind of natural therapies ... whether it

be herbal, homeopathic, or through nutrition and diet.

Interview 2

Most spoke about a careful weighing of the alternatives when reporting on their initial reactions to the recommended delay. For example, despite being in pain, one participant's desire to avoid orthodox medication meant that delay was eventually recognised as appropriate:

I was in quite a lot of pain, I thought, well, OK, I can wait, I'll give it, you know, I'll give it 4 or 5 days and then see if I get any better, and, and I did get better and ... cause I don't take painkillers in general ... I didn't bother with the prescription and I haven't had cystitis since.

Interview 9

Perhaps unsurprisingly, a weighing of the alternatives often involved a reflection on the potential for side effects (in particular thrush):

Well, I sort of sat there and went, oh, not 3 more days, but then when I thought about the side effects, it was like, well ... do I really want the side effect [of thrush] ... then that's going to be another 3, 4 days ... of more pain in the same area and I just thought, well, you know, because he was saying well, you've had it for 7 days and if you wait another 3 it will hopefully have gone anyway.

Interview 14

For one participant, the 'alternative' did not work and was described as unpleasant, but that did not appear to shake her enthusiasm for trying an alternative to antibiotics:

I was quite happy about that actually because I didn't want to take the antibiotics ... but just a bit disappointed it didn't work.

Interview 12

There were, of course, participants who remained symptomatic and elected to then take the delayed medication. For example, one participant commented that she had waited for 1 week and when still symptomatic took the antibiotic: 'I was trying to be really good!' (interview 7). Notably, there was some indication that participants did not always know how long they ought to wait to take the 'delayed prescription'.

Just one participant explicitly mentioned that the recommended delay was acceptable because of her

'faith' in her GP: 'I have a great deal of faith in my GP ... and because he was happy to suggest the Uvacin, I was happy to accept that' (interview 6). Others sought comfort from the knowledge that a 'backup' antibiotic was waiting at reception for them:

I guess in the back of my mind there was a slight reassurance that if all else fails I've got it [the prescription].

Interview 6

Well I understood I was doing this survey which would help ... I felt OK cause I knew that the prescription was there if I needed it.

Interview 20

Moreover, receiving an antibiotic prescription seemed to contribute to participants' feelings that their symptoms had been validated and taken seriously.

Negative experiences

The negative experiences associated with antibiotic delay were in part related to participants' concerns that their knowledge and experience of their bodily changes had not been taken seriously: 'I'm quite willing to listen, but I know my own body' (interview 8). For some, delay was alarming because their symptoms had, in their opinion, 'just gone past the waiting point'. One participant described her reaction to the proposed delay and how she finally decided to take the medication:

I think probably at the time I just thought well I've waited this long, I've done all the help, self-help measures myself, um ... the fact that he was asking [slight laughter] me to delay even longer was, oh, I don't want to do this but I think I did and then I think it got to the stage where I just thought no.

Interview 17

Another reported how she had delayed but then had returned to the doctors to get different antibiotics. The previous ones 'didn't work' and it had got to the stage where she 'couldn't work' (interview 11). She expressed the opinion that had she not delayed she could have 'got rid of it a lot sooner and gone back to work, instead of missing time at work'.

Interviewee 8 reported how 'it had gone past the waiting stage'. Indeed, she did not delay, as recommended, because it was interfering with her work. She reported that she was in 'terrible pain and it was frightening' and 'I was nearly in

tears'. It was clear from this particular account that the participant did not 'feel' validated in her complaint. For her there seemed to be a conflict between the patency of her condition and the GP's recruitment goals: 'he was more sort of pushing me to do the study and I was more just, no, I want to get it sorted out straight away'.

Similarly, interviewee 11 indicated that she felt that her needs were relegated in favour of the needs of the study:

I thought [the doctor] was more interested in telling me about [slight laugh] about your study ... and ... he really didn't want me to have ... [he was] a bit blasé about it and um ... I thought I told him ... I was sort of passing blood ... and it just annoyed me the fact that he didn't do anything with the first sample that I gave him.

Interview 11

Proper explanation of treatment options and validation of patient complaints or symptoms are potentially crucial to the success of 'backup' strategies. Most patients had tried lay remedies and waited to see if those remedies worked. Hence, it is unsurprising that some may see a recommendation for further delay as discrediting. Delaying antibiotic medication may signal to patients a rejection of their symptoms and denied entry to the 'sick role'.

Overall, however, the strategy of delay met with approval. Patients' expectations did not seem to revolve around their health-care professional's prescription notepad. Rather, expectations centred on being understood (and believed) and in being helped to understand the basis for their doctor's recommendations. Findings from this study suggest that some of the research literature and some health-care professionals overestimate patient demand for antibiotics in the case of UTI. Some patients might also overestimate the desire of health-care professionals to prescribe:

We know that viral infections don't necessarily respond to antibiotics but I do think that there is a general feeling out there that a lot of GPs will just go yeah here's a course of antibiotics just to get you out of the door and move on to the next one.

Interview 2

The causes of urinary tract infection

All participants were asked what they thought caused UTI. *Table 30* in Appendix 5 illustrates the range of causes offered by participants.

Overall, quite basic educational resources need to be made available in surgeries. In total, 15 of the 20 women interviewed discussed previous experiences of UTI/cystitis and yet when asked to discuss the nature and causes of UTI many struggled. There needs to be increased opportunities for patients who attend with a suspected UTI to discuss the nature and cause of the condition and the evidence (and uncertainty) about the utility of antibiotic medication.

It is interesting to note that 'lifestyle' explanations were frequently cited as contributing to UTI. Refraining from unhealthy behaviours, such as 'drinking caffeine', 'not drinking too much wine' and not being 'negligent' when it comes to cleanliness, were all frequently cited. Participants spoke in terms that invoked a 'duty to stay healthy' and to consume a lifestyle of self-discipline (good diet, exercise and appropriate self-care strategies when faced with symptoms). In a period when 'lifestyles' have been fully commercialised,⁶⁷ it is unsurprising to find that participants spoke in these terms, but the implications of such thinking must be borne in mind. As Blaxter⁶⁹ suggests, one implication may be that the cause of illness may be construed as indicative of personal weakness and even lack of control.

Finally, the majority indicated some discomfort when asked about the nature and causes of UTI. The social context of the interviews may have influenced this more so than other questions. The question may have been viewed as a 'test' in which participants could be right or wrong. Indeed, answers were often prefaced or closed with the phrase 'I don't know' or some similar epistemic downgrade. Nevertheless, it did seem that there was room for greater educational resources for, and discussion with, patients presenting with UTI.

Discussion

The journey from 'person to patient'

In her study of patient pathways from 'person to patient', Zola⁶¹ reported the importance of doctors paying attention to the 'specific trigger which forced or which individuals used as an excuse to seek medical aid'. She noted that no attention to such triggers resulted in the 'greatest likelihood of that patient eventually breaking off treatment'.

This interview study has explored and highlighted the considerable amount of work that goes on

behind the scenes on the journey from 'person to patient'. This includes the initial symptom onset, the process of symptom recognition, moments when action is taken, periods of waiting and, finally, seeking medical help. When patients are being asked to delay taking antibiotic medication and essentially being asked to 'wait some more', the sometimes protracted, uncomfortable and worrying journey needs to be acknowledged. Without such acknowledgement there is a danger that patients will leave the consulting room without feeling validated in their experiences and concerns.

Further, although common it is important to recognise that UTI may be alarming and the nature and cause of the symptoms uncertain. Even those women with a previous experience expressed how sometimes there is no such thing as 'normal'; each episode has the potential to be qualitatively different. In such circumstances it may be that even the 'experienced' UTI 'patient' may require reassurance, discussion and, perhaps, explanation about the causes of (and strategies for preventing) UTI. A fear of spread to the kidneys and the appearance of blood in the urine were two organic symptoms that triggered worry and, in turn, women to seek help. The generalised impact of symptoms on vocational and leisure activities was not inconsiderable and women expressed these as important triggers for help seeking.

The experience of delay

The few who experienced delay negatively indicated that they had not felt validated in their experience and were threatened by such delay because the rationale for not taking the antibiotics was not crystal clear. Over 30 years ago Zola⁶¹ indicated the importance of attending to the broader contexts of 'patients' lives. She noted that:

the physician may more intelligently intervene in the patient's efforts to cope with his disorder if he has the knowledge and awareness of the patient's views on health, sickness, his expectations and his reasons for seeking help.

Conclusion

If women are asked to delay taking antibiotics, great care is needed in both acknowledging the triggers to consult and particular worries and explaining the rationale for not using antibiotics immediately.

Chapter 7

Suggestions for further research

- The evidence from this series of validation studies suggests that dipsticks alone have limited NPV. Research into the value of microscopy in practice (used in Scandinavian countries) could assess whether the predictive values could be improved.
- The issue of the gold standard for diagnosing UTI could helpfully be resolved by either large observational studies or trials, by assessing the threshold of colony counts at which antibiotics or alternatively antibiotic resistance make any difference to symptoms.
- The preliminary evidence of the cost-effectiveness of the use of dipsticks could be confirmed in a much larger study that assesses the issue of medicalisation in the longer term and which involves the modelling of the impact of attendance and antibiotic use on antibiotic resistance. Qualitative work will provide valuable insights alongside any further trial. Such qualitative work would helpfully occur at the development stage of such a trial.
- An economic study that documents quality of life in UTI using conventional quality of life measures is indicated. These measures could be related to symptomatic outcomes from the trial data, and modelling would then allow the likely cost-effectiveness of different strategies to be further explored.
- Dipslides are little used in current practice but do have the potential to be used in primary care. To maximise the utility of dipsticks whilst taking account of the poor NPVs documented in this study, we suggest trialling a combined strategy: empirical treatment for positive dipstick and a dipslide for negative results; the dipslide is read the next day and any positive specimens are then treated. This combined strategy should improve the targeting of treatment and minimise the increase in costs of using dipslides.
- A placebo-controlled trial of antibiotics in patients who have both a negative dipstick and also negative dipslides (this study could potentially be combined with the study proposed above; this would assess whether intracellular infection is likely to be significant).
- The results indicate that a trial to assess the symptomatic benefit of herbal products could be useful.

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Contribution of authors

All authors contributed to the design, management and write-up of this study. In addition, PL was the chief investigator, led the grant application and provided overall co-ordination for the study; ST coordinated and managed the study on a day-to-day basis; KR managed the data and the data base; GW and MM co-ordinated local practice

recruitment and retention; AL co-ordinated the lab work; DT co-ordinated the economic analysis; GL co-ordinated the qualitative study; AA co-ordinated the follow-up data; and both MM and PL co-ordinated the statistical analyses.

Publication

Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes A, *et al.* Can urinary tract infection (UTI) be predicted in primary care settings? The sensitivity and specificity of Near Patient Tests (NPTs) and clinical scores in adult women with suspected UTI. *Br J Gen Pract* 2006;56:606–12.

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Appendix I

Implications of using dipstick and clinical information, and different laboratory standards

TABLE 24 Combined clinical and dipstick score to predict diagnosis of urinary tract infection^a

Cut-point (% at or above cut- point)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Correctly classified (%)	LR +ve	LR -ve
≥0 (100)	100	0.00			62.25	1.00	
≥0.5 (93)	98.03	14.94	65.53	82.14	66.67	1.15	0.13
≥1 (89)	96.06	22.08	67.03	77.27	68.14	1.23	0.18
≥1.5 (81)	92.13	37.01	70.69	74.02	71.32	1.46	0.21
≥2 (73)	88.98	53.25	75.84	74.54	75.49	1.90	0.21
≥2.5 (68)	86.22	61.69	78.78	73.07	76.96	2.25	0.22
≥3 (57)	75.59	74.03	82.76	64.77	75.00	2.91	0.33
≥3.5(48)	64.17	78.57	83.16	57.07	69.61	2.99	0.46
≥4 (31)	44.09	90.26	88.19	49.47	61.52	4.53	0.62
≥4.5 (16)	23.62	96.75	92.30	43.44	51.23	7.28	0.79
≥5 (12)	18.9	98.70	96.00	42.46	49.02	14.55	0.82
≥5.5 (9)	13.78	100.00	100	41.29	46.32		0.86
≥6 (6)	9.45	100.00	100	40.01	43.63		0.91
> 6 (0)	0.00	100.00			37.75		1.00

^a Based on sum of nitrite = 2 according to European guidelines standards, leucocyte = 1.5, haematuria = 1, moderately severe dysuria = 1, moderately severe nocturia = 0.5.
The score from these variables weighted according to the rounded logistic coefficients has an area under the receiver operating curve of 0.80 (95% CI 0.76–0.85)

Combined clinical and dipstick score When clinical and dipstick variables are combined, five variables predict UTI: nitrite (6.43; 95% CI 2.75–15.0, $p < 0.001$), leucocytes (3.68; 95% CI 2.17–6.25, $p < 0.001$), blood (2.13; 95% CI 30–3.50, $p = 0.003$), moderately severe dysuria (2.13; 95% CI 1.31–3.45, $p = 0.002$) and moderately severe nocturia (1.73; 95% CI 1.07–2.78, $p = 0.024$). A cut-off of 3 or more in a score weighted according to the sum of the rounded logistic coefficients has a sensitivity of 76% (192/254) and specificity of 74% (114/154), i.e. not much better than dipsticks alone.

Using clinical and dipstick scores sequentially For those with a clinical score of 0, 48/68 (71%) do not have

an infection, and for those with a score of 3 or more, 78/93 (84%) have an infection. If dipsticks are used in the remaining patients then the overall performance of this approach achieves a sensitivity of 78.03% (206/264) and a specificity of 70.73% (116/164), with 78.9% of people correctly classified, LR +ve test 2.67 and LR -ve test 0.31, i.e. not performing much better than dipsticks alone.

Implications of using a different gold standard Using the standard of $\geq 10^5$ cfu/ml the clinical score had an area under the receiver operating curve of 0.69 and the dipstick score had an area under the receiver operating curve of 0.74.

TABLE 25 Dipstick rule: performance in predicting diagnosis of urinary tract infection (UTI) using laboratory cut-off of $\geq 10^5$ cfu/ml

Standard	Test ^a		Total
	Dipstick –	Dipstick +	
UTI –	133	98	231
UTI +	33	144	177
Total	166	242	

a Positive test: either nitrite or blood and leucocytes.
Sensitivity = 144/177 = 81.4% (95% CI 75.7–87.1%); specificity = 133/231 = 57.6% (51.2–64.0%);
PPV = 144/242 = 59.5% (53.3–65.7%); NPV = 133/166 = 80.1% (75.0–86.2%); LR +ve test = 1.92 (1.62–2.26); LR –ve test = 0.32 (0.23–0.45).

TABLE 26 Clinical rule: performance in predicting diagnosis using laboratory cut-off of $\geq 10^5$ cfu/ml

Standard	Test ^a		Total
	Score –	Score +	
UTI –	140	91	231
UTI +	56	121	177
Total	196	212	

a Positive test: two or more of moderately bad dysuria, moderately bad nocturia, urine smell offensive, urine cloudy.
Sensitivity = 121/177 = 68.4% (95% CI 61.5–75.3%); specificity = 140/231 = 60.6% (54.3–66.9%);
PPV = 164/212 = 57.1% (50.4–63.8%); NPV = 140/196 = 71.4% (65.3–76.5%); LR +ve test = 1.74 (1.44–2.10); LR –ve test = 0.52 (0.41–0.66).

TABLE 27 Reporting based on STARD initiative⁷⁰

1. Title, abstract and key words	Page 1
2. Research question or aims	Page 1–2
3. Describe participants, inclusion criteria	Page 2
4. Recruitment mechanisms	Page 2
5. Participant sampling (e.g. consecutive)	Page 2
6. Data collection (prospective or retrospective)	Page 2–3
7. Describe reference standard and its rationale	Page 2
8. Describe technical specifications	Page 2
9. Definition and rationale for cut-off points of index test and standard	Page 2–3
10. Describe the number training of staff performing tests and standard	Page 2
11. Were the readers of the index test blinded?	Page 2
12. Describe the methods for calculating or comparing measures and describing uncertainty	Page 3
13. Describe methods for calculating reproducibility (if carried out)	N/A
14. Report when the study was carried out	Page 2
15. Report clinical and demographic details	Page 3
16. Report how many participants did not undergo the index test/standard	Page 3
17. Report time intervals between index test and standard	Page 3
18. Report severity of disease in those with and without target condition	Page 3
19. Cross-tabulation of index test by results of standard	Tables 1 and 3
20. Report any adverse events (test or standard)	N/A
21. Estimates of diagnostic accuracy and of uncertainty (confidence intervals)	Tables 1 and 2
22. Report how indeterminate results missing responses and outliers were handled	There was no modification of results if indeterminate results or missing values occurred
23. Report estimates of diagnostic accuracy between readers	N/A
24. Report estimates of reproducibility if carried out	N/A
25. Discuss clinical applicability of study findings	Pages 4 and 5

Appendix 2

Reporting of validation testing study

1. Title, abstract and key words	Page 1
2. Research question or aims	Page 1–2
3. Describe participants, inclusion criteria	Page 2 and 9
4. Recruitment mechanisms	Page 2
5. Participant sampling (e.g. consecutive)	Page 2
6. Data collection (prospective or retrospective)	Page 2–3
7. Describe reference standard and its rationale	Page 2
8. Describe technical specifications	Page 2
9. Definition and rationale for cut-off points of index test and standard	Page 2–3
10. Describe the number training of staff performing tests and standard	Page 2
11. Were the readers of the index test blinded?	Page 2
12. Describe the methods for calculating or comparing measures and describing uncertainty	Page 3
13. Describe methods for calculating reproducibility (if carried out)	N/A
14. Report when the study was carried out	Page 9
15. Report clinical and demographic details	Page 9
16. Report how many participants did not undergo the index test/standard	Page 9
17. Report time intervals between index test and standard	Page 3
18. Report severity of disease in those with and without target condition	Table 7
19. Cross-tabulation of index test by results of standard	Tables 7–11
20. Report any adverse events (test or standard)	N/A
21. Estimates of diagnostic accuracy and of uncertainty (confidence intervals)	Table 9
22. Report how indeterminate results missing responses and outliers were handled	There was no modification of results if indeterminate results or missing values occurred
23. Report estimates of diagnostic accuracy between readers	N/A
24. Report estimates of reproducibility if carried out	See Chapter 2
25. Discuss clinical applicability of study findings	Page 12

Reporting based on the STARD initiative.⁷⁰

Appendix 3

The five management strategies representing common approaches

- *Empirical antibiotic treatment* This is the most common strategy in practice and was used as the control group. Patients were prescribed an antibiotic (trimethoprim 200 mg twice a day for 3 days). If patients were allergic to trimethoprim they were offered an alternative (cefaclor or cefalexin) as this is not a trial of antibiotics per se but a trial of management/ advice strategies.
- *Empirical delayed antibiotics* All patients were advised to drink plenty and were offered a delayed antibiotic prescription to be used if symptoms did not start to improve after 48 hours (doctors were asked to leave a prescription at the front desk for patients to collect as necessary or could negotiate with the patient if they wanted to take the prescription away). The rationale for this group is that 40% of patients with suspected UTI do not have infection and, even in those with laboratory-diagnosed infections, the illness is likely to be self-limiting.^{28,71}
- *Symptom score*⁴² Patients who had two or more of the following four features were offered immediate antibiotics, i.e. symptomatic treatment only: urine cloudy on examination, urine offensive smell on examination, patient report of moderately severe dysuria, patient report of moderately severe nocturia. From the previous study⁴² we estimated the sensitivity of this symptom score approach as 68% and so patients without two or more features were also offered a delayed antibiotic prescription to use if their symptoms did not settle after 48 hours.
- *Dipstick* Patients who had either nitrites or leucocytes and a trace of blood were offered antibiotics initially. Patients not fulfilling the above criteria (which we estimate had a sensitivity of 71%⁴²) were offered a delayed antibiotic prescription to use if their symptoms did not settle after a few days.
- *Treatment guided by MSU result* This was the only group in which an MSU was carried out routinely. Patients were offered symptomatic treatment until the results of the MSU were known. This is the 'reference' method of diagnosing infection and of targeting antibiotic use.

Appendix 4

Self-help advice components

The following advice components were randomised:

- *Leaflet versus no leaflet* We have piloted and developed a patient information leaflet based on a previous small pilot study and existing evidence,³⁰ which has been reviewed by the Plain English Campaign. The leaflet contains information about the causes of UTI, prevention, self-help measures and when to see the doctor.
- *Advice to use commercial cranberry juice versus orange juice versus water*⁷² All patients were advised to drink at least 3–4 litres per day and to make at least 1 litre of this the relevant fruit juice if appropriate.
- *Advice to use over-the-counter bearberry extract (e.g. Uvacin) versus no extract*⁷³ Patients were advised to purchase extracts from local pharmacies or health food shops.
- *Advice to use bicarbonate versus no bicarbonate* Patients were advised to make up a bicarbonate solution several times per day masked with squash or equivalent.³⁰

Appendix 5

Data tables from qualitative study

TABLE 28 Summary of volunteered signs/symptoms

Symptom	Frequency
Physical	
Frequency	8
Very painful/severe/bad	7
Bleeding	6
Cold/flu-like symptoms/temperature	4
Backache/pain	3
Stinging/burning/stabbing	3
Pains/balloons in tummy	3
Uncomfortable	3
Poor concentration	2
Pain on urinating	2
Smelly urine	2
Tired/exhausted	2
Sleeplessness	1
Hot sensation in bladder	1
Pain worsening	1
General/emotional/functional	
Generally unwell/lousy/poorly	6
Normal duties disrupted/debilitating	3

TABLE 29 'Wait and see' strategy

Days waited before visiting GP	Interview
1 night and 1 day	Interview 18
2–3 days	Interviews 8, 11–13, 15 and 17
4 days	Interview 6
7 days	Interviews 7, 9, 14, 16 and 20
10 days	Interview 4
3 weeks	Interviews 2 and 19
4 weeks	Interview 1
Unclear	Interviews 3, 5 and 10

TABLE 30 Causes of urinary tract infection (mix of participants' precise words in quotations and authors' summary)

Interview number	What causes a urinary tract infection?
1	Wiping the wrong way; low immunity and antibiotics
2	Once you have had it tend to be more susceptible; sex, diet and lifestyle. Wine and drinking Bovril caused 'mine'
3	Age; 'drying up'; 'penalty of growing old'. Long bicycle ride on holiday and sitting on damp towel
4	Deviant case; interstitial cystitis
5	Dehydration; infection following diarrhoea; age – 'have to be more careful as get older'; stress
6	Dehydration; alcohol; enhanced sexual activity; being on holiday
7	'Don't know really' – drugs and antibiotics? People go through 'phases'
8	Dehydration; sex; perfumed products; 'that's all I know'
9	'I'm not sure really'; 'I think some of it is cleanliness ... I sit for [prolonged periods] and [toilet breaks are very quick] You leave it until you have to go'
10	'I'm a bit perplexed about it cause it's something that I never had ... growing up I've heard that it's associated with the menopause I assume it can be caused by your sex life ... or some irritation. I've been told that it's ... a germ and it can be caused by a germ in the water'. Individual cause: 'doesn't seem to be any one particular cause'
11	A bug? Wiping the wrong way, tight clothes 'or am I just making that up'. Individual cause: 'I don't know in my case what [causes it], because I don't think I've been doing anything different ... to suddenly get it at my age and not ever had it before ... I don't know'
12	'I've read loads on it; I should know (laughter from both). I've had all the books out. Every time something goes wrong I read all the books ... I don't know ... it's ... I don't know, I can't think of it now'
13	Active sex life
14	'I don't know ... sometimes if I've ... become sexually active, I always get cystitis ... 100% I can guarantee it. Hence I just don't bother anymore (laughter). No, go away, because I know I'm going to get ... it tends to be around my period that I get it ... it's yeah, if I'm, if I'm, if I'm in a relationship, it's a, it's a definite (laughter) ... it's kind of inconvenient, but you know'
15	Individual cause: 'I feel that it is actually just a bit of, well, a bit of bad luck and perhaps a little bit of lack of concentration [when going to the loo], because I do remember ... being a little less careful than I should normally have been'; 'negligence'; 'the more stressed you are the more it ... makes your body vulnerable. I think it lowers your body's resistance in so many ways'
16	'People don't drink enough ... I think in this case, that is maybe what led to mine ... and not going to toilet when you need to, you hold on a lot. I think perhaps those two things do contribute to it a great deal'
17	Pregnancy, hormones, menstruation, Tampax (irritation not infection), sex (aggravation)
18	The doctor 'told me it was to do with sexual activity, so I presume that's what it was because things had changed in my life which I explained to her'
19	A highly moral discourse again: 'I will be prepared to admit it's my own fault (laughter) cause I'm terrible, I just, coffee addict and ... I just hardly every drink water ... I'm trying ... to do better'; 'I did have a really hot temperature ... I didn't know whether I was having hot flushes ... I'm 44 (slight laughter) I thought, oh, maybe I might be having the change'
20	'Not drinking enough'

TABLE 31 Participants' reasons for the 'no delay' decision

Interview	Reason for the 'no delay' decision
4	Interstitial cystitis
10	He didn't suggest waiting because 'I was in such a state'
13	She told the doctor what she wanted and did not delay or try Uvacin
16	No delay recommended: 'she felt in this case, because I'd already ... tried other courses of action and that was 7 days and the symptoms were becoming more severe rather than better, that antibiotics was probably the right course of action to take'
18	Tried antibiotic and it did not work. Then had to try another type
19	Given antibiotic immediately for immediate use

Appendix 6

Interview guide prompts for urinary tract infection

1. What led you to come and see the doctor/nurse with your urinary infection/urinary inflammation?
 - (bv) Severity
 - (bw) Duration
 - (bx) Self-help – tried, if so, what, e.g. potassium citrate, Uvacin
 - (by) Previous experience of urinary tract infections
 - (bz) Previous experience of seeing doctor and getting treatment
 - (ca) Family/friend/social support network
2. What do you think causes urine infections?
 - (cb) Bacteria (if so, where from?)
 - (cc) Fluid intake
 - (cd) Sexual intercourse
 - (ce) Hormones (e.g. pill, hormone replacement therapy) (are you on them?)
 - (cf) Weak system – past/family history
3. Have you previously had antibiotics?
 - (cg) What do you feel about them?
 - (ch) Have you heard about problems with antibiotics (e.g. resistance, side effects)?
4. What did you feel about the consultation that you had?
 - (ci) Sympathetic
 - (cj) Enough information
 - (ck) Clear advice
5. Do you remember the advice that you were given about antibiotics?
 - (cl) Were you advised to wait and, if so, how long?
 - (cm) How long did you wait?
 - (cn) What was your experience of waiting?
 - (co) If you started antibiotics, why? (e.g. severity of symptoms, going on, coping with life)
6. Did the doctor/nurse take a urine sample and test it or send it for testing?
 - (cp) If yes, what do you think about this?
 - (cq) If no, what do you think about this?
7. Were you given self-help advice or a self-help leaflet?
 - (cr) If so, what, and what did you think about it?

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