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Original article

Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial

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ABSTRACT

Objectives: The aim was to investigate if offering symptomatic therapy (Uva-ursi or ibuprofen) alongside a delayed prescription would relieve symptoms and reduce the consumption of antibiotics for adult women presenting with acute uncomplicated urinary tract infection (UTI).
Methods: A 2 × 2 factorial placebo controlled randomized trial in primary care. The participants were 382 women aged 18–70 years with symptoms of dysuria, urgency, or frequency of urination and suspected by a clinician to have a lower UTI. The interventions were Uva-ursi extract and/or ibuprofen advice. All women were provided with a delayed or 'back-up' prescription for antibiotics. Missing data were imputed using multiple imputation methods (ISRCTN registry: ISRCTN43397016).
Results: An ITT analysis of mean score for frequency symptoms assessed on Days 2–4 found no evidence of a difference between Uva-ursi vs. placebo −0.06 (95% CI −0.33 to 0.21; p 0.661), nor ibuprofen vs. no ibuprofen advice −0.01 (95% CI −0.27 to 0.26; p 0.951). There was no evidence of a reduction in antibiotic consumption with Uva-ursi (39.9% vs. placebo 47.4%; logistic regression odds ratio (OR) 0.59 (95% CI 0.22–1.58; p 0.293) but there was a significant reduction for ibuprofen advice (34.9% vs. no advice 51.0%; OR 0.27 (95% CI 0.10 to 0.72; p 0.009). There were no safety concerns and no episodes of upper tract infection were recorded.
Conclusions: We found no evidence of an effect of either intervention on the severity of frequency symptoms. There is evidence that advice to take ibuprofen will reduce antibiotic consumption without increasing complications. For every seven women given this advice, one less will use antibiotics.
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Introduction

Acute cystitis is one of the most frequent triggers of consultation in women in primary care. The lifetime risk in women is 50% and the annual incidence is over 10% [1]. It accounts for between 1% and 3% of consultations and results in an antibiotic prescription for the majority of women (93%) [2]. A meta-analysis of five randomized trials of antibiotic/placebo confirmed greater symptomatic and bacteriological cure with antibiotic treatment but with only a modest effect on duration of symptoms [3]. Many women presenting with symptoms of urinary infection will not have a bacteriologically proven infection on culture [4] and most complaints will be self-limiting [5]. However, while women are open to

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alternative approaches to treatment [6], to dispense with antibiotic treatment would require an appropriate approach to dealing with the burden of symptoms and responding to women's suffering by offering alternative symptomatic treatments [6,7].

Two alternative treatments for symptomatic relief have been identified, namely ibuprofen and *Arctostaphylos uva-ursi* (L.) Spreng. (Ericaceae) leaf extract, a plant found in the mountains of the Northern Hemisphere with a long history of use in western herbal medicine, hereafter abbreviated to "Uva-ursi" [8]. The evidence suggests that NSAIDs may provide symptom relief and reduce antibiotic use, but there is also suggestive evidence that they may increase subsequent upper tract infections [9–11]. Uva-ursi was not tested in randomized trials [8]. We proposed to test whether offering these symptomatic therapies alongside a delayed prescription would provide symptomatic relief and reduce the consumption of antibiotics.

Methods

The methods are described in full elsewhere [8]. ATAFUTI is a multicentre, factorial (2 × 2) design, including a randomized double-blind placebo-controlled trial of Uva-ursi, and open pragmatic trial of advice/no advice to take ibuprofen. Recruitment took place in primary care settings across the UK.

Treatments were allocated at random by prior randomization of treatment packs using block randomization, with no stratification factors, into one of four groups:

- Group 1 Uva-ursi + advice to take ibuprofen
- Group 2 Placebo + advice to take ibuprofen
- Group 3 Uva-ursi + no advice to take ibuprofen
- Group 4 Placebo + no advice to take ibuprofen.

We recruited adult women presenting with symptoms of non-complicated acute UTI. Consenting participants were asked to provide a urine specimen for bacterial analysis at baseline, were asked to take the study medication for 3–5 days and to complete a symptom diary for up to 2 weeks. All participants were issued a prescription for antibiotics to be delayed and used if symptoms worsened, or after 3–5 days if symptoms failed to improve. A GP notes review was completed after 3 months to record re-consultations with further urinary symptoms.

Patient public involvement

Two patients/public representatives were involved in the study design and development of the study materials, attended trial steering group meetings, and helped with interpretation of the results.

Participants' eligibility

Inclusion

Women (aged 18–70 years) who upon presenting to primary care with dysuria, urgency, or frequency of urination were suspected by a GP or nurse practitioner to have a lower urinary tract infection.

Exclusions

Criteria for exclusion were known or suspected pregnancy; breast feeding; suspected upper urinary tract infection (presenting with back pain, fever >38°C, systemic illness); patients requiring immediate antibiotics; are within 7 days of taking antibiotics; frequent recurrent UTI (>3 UTI episodes in past 12 months); known contraindications or cautions to ibuprofen; using an NSAID or taking an Uva-ursi preparation and unwilling or unable to discontinue for the study period; diabetes; an immunodeficiency state or on long-term corticosteroids or chemotherapy; bladder surgery including cystoscopy in the last 4 weeks; currently taking warfarin, or a defect of the blood clotting system; recruited to another trial in the previous 4 weeks.

Participants and clinicians were blinded to the Uva-ursi groups. Recruiting practitioners were blinded to the ibuprofen recommendation prior to opening the pack, and endorsed ibuprofen use only when directed after opening. Outcome assessors were blind to allocation. The randomization sequence was generated by the study statistician and communicated to the manufacturer of the study medication.

Study interventions

The investigational medicinal product comprised Uva-ursi extract containing 20% arbutin with a matching placebo containing sugar beet fibre (Fibrex®), an inert substance with a similar colour, and a herbal flavour. The total daily dose of Uva-ursi was 3600 mg which was divided across three capsules to be taken orally three times a day (Table S1 for details of herbal intervention). Participants were asked to take the study medication between 3 and 5 days (stopping if symptoms had improved). A prescription for back-up antibiotics was provided to participants with instructions to take if adequate symptom relief was not obtained from the study medication.

A structured advice sheet and card detailing the ibuprofen dose was provided to participants randomized to the ibuprofen arm. A daily dose of 1200 mg, to match the dose used in the previous trials, was recommended or prescribed on request [9,12].

Assessment and follow-up

Participants were requested to complete a daily symptom diary used in previous studies of UTI detailing severity of their urinary tract symptom(s) [4,13,14]. The diary scale recorded symptom severity on a seven-point scale ranging from 0 to 6; 0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderate problem, 4 = bad problem, 5 = very bad problem, and 6 = as bad as it could be). Participants were contacted by telephone after 3 days to assist completion and in the event of delayed return of the diary, to prompt return or to complete a brief symptom inventory.

Primary outcome

Mean frequency symptom severity score on Days 2–4 using 14-day validated diary data [4,13–15]. This is defined as the mean score of the frequency symptoms (burning, urgency, daytime frequency, and night time frequency), recorded on Days 2, 3, and 4.

Secondary outcomes

The secondary symptoms included mean unwell symptom severity score on Days 2–4, duration of moderately bad or worse symptoms, and mean global symptom severity score using 14-day validated diary data [4,13–15]. Use of antibiotics and re-consultation (full details in web supplement).

Exploratory analysis

Differential effects on primary outcome depending on culture confirmation of urinary tract infection were aligned to European standards [16]. Infection was defined as any growth of bacteria in the urine culture results.

Power calculation and statistical analysis

In our previous study the severity of frequency symptoms at 2–4 days was 2.15 (SD 1.18) in the immediate antibiotic group and 2.11 (mean difference −0.04 95% CI −0.47 to 0.40) in the delayed antibiotic group [13], based on severity of frequency symptoms in the delayed antibiotic group [13] and the clinically significant change in symptom severity of 0.5. For the 2 × 2 factorial design, to detect a mean severity difference of 0.5 with SD 1.18 required a sample of 60 per group. We further increased the sample size to take into account the numbers needed to demonstrate a reduction in antibiotic use, a key secondary outcome, and hence the initial

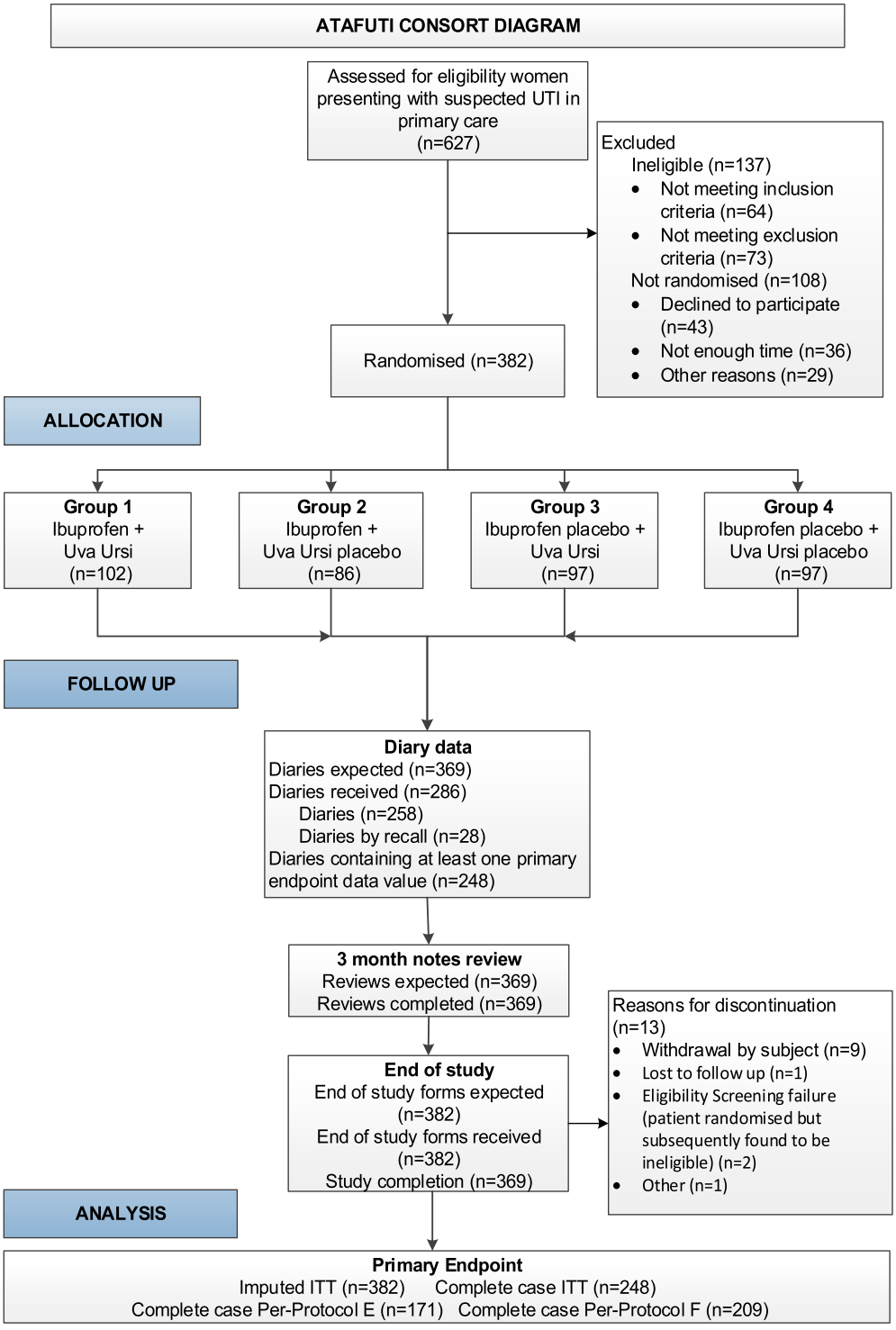

Fig. 1. Patient flow in the study.

target was set at 328 (four groups of 82 patients) (for a full explanation please see supplementary material). We noted the loss to follow-up was higher than anticipated and amended the required sample to 376 patients (94 per group). The trial was not powered for any interaction between factorial groups.

Statistical analysis

Owing to missing data, for the primary endpoint analysis and some key secondary endpoint analyses, a hierarchical manual imputation process was first carried out on any missing symptom severity values on days either side. After the manual imputation process, multiple imputation was performed.

For the primary outcome, analysis of covariance was used to analyse the imputed mean frequency symptom severity data on Days 2–4 adjusting for the baseline symptom severity score and age. This analysis was repeated adjusting also for the use of antibiotics. Logistic regression was used for dichotomous outcomes (antibiotic use, re-consultation in 1 month with UTI, and re-consultation within 3 months with UTI from notes review) adjusting for age on records with complete data. Negative binomial regression was used to analyse duration of moderately bad symptoms adjusting for age, performed on records with complete data, as stipulated in the pre-specified analysis plan.

All analyses were also carried out on a per-protocol basis in accordance with patients' compliance with Uva-ursi and ibuprofen.

Results

Recruitment is detailed in Fig. 1. Participants were well matched at baseline (Table 1). Withdrawal data are shown in Table 2. After telephone contact, 248 of the returned diaries contained sufficient information for the complete case primary endpoint analysis (248/382; 65%). The primary endpoint analysis of covariance of frequency symptom severity on Days 2–4, adjusting for baseline frequency symptom severity, incorporating multiple imputed data (ITT population B, $n = 382$), gave no evidence of a difference in symptom severity between the factorial groups (Table 3): Uva-ursi −0.06 (95% CI −0.33 to 021; p 0.661); ibuprofen advice −0.01 (95% CI −0.27 to 0.26; p 0.951). Similarly when controlling for antibiotic use up to day 4, no differences were seen (Table 4). When considering the duration of moderately bad symptoms a negative binomial model did not show significant difference in recovery between groups: incidence rate ratio (IRR) for Uva-ursi vs. placebo 1.02 (95% CI 0.72–1.45; p 0.922), and ibuprofen advice vs. no advice IRR 0.87 (95% CI 0.62–1.24; p 0.453).

Antibiotic use

Antibiotic use in the first 2 weeks by participants (for whom this information is available) is reported in Table 5. Overall antibiotic use ranged considerably from 24 out of 70 (34.3%) in Group 1 (Uva-ursi + ibuprofen advice) to 42 out of 74 (56.8%) in Group 4 (placebo + no advice). For those receiving Uva-ursi use was 57 out of 143 (39.9%) vs. 63 out of 133 (47.4%) and those given ibuprofen advice 45 out of 129 (34.9%) vs. 75 out of 147 (51.0%). A logistic regression analysis for antibiotic use gave an odds ratio (OR) 0.59 (95% CI 0.22–1.58; p 0.293) for Uva-ursi and for ibuprofen OR 0.27 (95% CI 0.10–0.72; p 0.009) (Table 6). Using the unadjusted data, one less woman would use antibiotics in the following 2 weeks for every 6.8 women given ibuprofen advice (95% CI 4.2–18.0).

Per protocol analysis

When analysed per protocol, the primary endpoint was unaltered (Table S2). The per protocol analysis on the ibuprofen related per protocol population E ($n = 182$ with complete data) for antibiotic use gave similar estimates for the odds ratios but the effect was attenuated and no longer significant for ibuprofen: Uva-ursi odds ratio 0.81 (95% CI 0.22–3.01, p 0.756); ibuprofen OR 0.43 (95% CI 0.12–1.57, p 0.202) (Table S3).

Re-consultation

Re-consultation data collected from notes review showed that re-consulting with urinary tract infection symptoms was recorded in 58 out of 382 (15.2%) in the first month and 88 out of 382 (23.0%) in the 3 months following the index consultation (Table 7). Logistic regression analysis did not show any evidence of differences between the groups (data not shown).

Table 1
Baseline table.

Characteristic	Group 1[a] (Uva-ursi + Ibuprofen advice) ($n = 102$)	Group 2[a] (Placebo + ibuprofen advice) ($n = 86$)	Group 3[a] (Uva-ursi + No ibuprofen advice) ($n = 97$)	Group 4[a] (Placebo + No Ibuprofen advice) ($n = 97$)	Total ($n = 382$)
Age in years at baseline, mean (SD)	45.5 (15.16)	39.9 (15.48)	44.6 (16.10)	44.8 (14.29)	43.8 (15.36)
Symptom duration in days[b], median (IQR)	3.0 (2.0 to 5.0)	3.5 (2.0 to 6.0)	4.0 (3.0 to 7.0)	4.0 (2.0 to 6.0)	3.0 (2.0 to 6.0)
Patient's temperature, °C, mean (SD)	36.7 (0.45)	36.7 (0.50)	36.7 (0.42)	36.8 (0.41)	36.7 (0.44)
Urine culture infected, *n* (%)	19 (24.1%)	26 (37.7%)	23 (34.3%)	24 (32.4%)	92 (31.8%)
Experience of a urine infection in the last year, *n* (%)	30 (53.6%)	30 (58.8%)	32 (50.0%)	34 (51.5%)	126 (53.2%)
Frequency symptoms[c], *n*, mean (SD)					
All patients	102, 2.5 (1.23)	86, 2.6 (1.14)	97, 2.4 (1.13)	97, 2.4 (1.11)	382, 2.5 (1.15)
Patients **with** symptom diary return information available	59, 2.4 (1.20)	53, 2.5 (1.00)	67, 2.5 (1.08)	69, 2.4 (1.16)	248, 2.4 (1.11)
Patients **without** symptom diary return information available	43, 2.6 (1.26)	33, 2.7 (1.34)	30, 2.3 (1.23)	28, 2.5 (1.01)	134, 2.5 (1.22)

IQR, inter-quartile range; SD, standard deviation; MSU, midstream specimen of urine.

[a] Group 1 = Patients who received Uva-ursi and advice to take ibuprofen, Group 2 = Patients who received Uva-ursi placebo and advice to take ibuprofen, Group 3 = Patients who received Uva-ursi and no advice to take ibuprofen, Group 4 = Patients who received Uva-ursi placebo and no advice to take ibuprofen.

[b] Symptom duration is the time (in days) that the patient had current symptoms for. Information collected at baseline.

[c] Mean score of four items (burning, urgency, daytime frequency, night time frequency) as per primary outcome. t test comparing baseline frequency symptom score between patients with symptom diary return information available vs. patients without symptom diary return information available identified no significant difference between groups (p 0.359).

Table 2
Withdrawal information for the trial

Reason for withdrawal	Group 1[a] (uva-ursi + ibuprofen advice) ($n = 102$)	Group 2[a] (Placebo + Ibuprofen advice) ($n = 86$)	Group 3[a] (uva-ursi + No ibuprofen advice) ($n = 97$)	Group 4[a] (Placebo + No Ibuprofen advice) ($n = 97$)	Total ($n = 382$)
End of Study form present, *n* (%)	102 (100)	86 (100)	97 (100)	97 (100)	382 (100)
Completed study, *n* (%)	98 (96.1)	80 (93.0)	95 (97.9)	96 (99.0)	369 (96.6)
Did not complete study, *n* (%)	4 (3.9)	6 (7.0)	2 (2.1)	1 (1.0)	13 (3.4)

[a] Group 1, patients who received Uva-ursi and advice to take ibuprofen; Group 2, patients who received Uva-ursi placebo and advice to take ibuprofen; Group 3, patients who received Uva-ursi and no advice to take ibuprofen; Group 4, patients who received Uva-ursi placebo and no advice to take ibuprofen.

Results of urine culture subgroup

A pre-planned subgroup analysis for the primary endpoint excluding those without evidence of infection on the urine culture (with infection $n = 92$) did not alter the inferences for symptom severity (when adjusting for antibiotic use up to day 4): Uva-ursi −0.17 (95% CI −0.64 to 0.30; p 0.476); ibuprofen 0.22 (95% CI −0.29 to 0.73; p 0.401).

Harms

No episodes of upper tract infection were documented in any group (for all patients 95% CI 0–0.00961). There were two SAEs reported in trial participants, both were hospital admissions. The first episode was an abdominal wall abscess; this occurred in a patient within the Uva-ursi and the no advice to take ibuprofen group and was considered unlikely to be related to treatment. The second was right iliac fossa pain; this occurred in a patient within the Uva-ursi placebo and no advice to take ibuprofen group and was not considered to be related to treatment.

Discussion

Summary of main findings

There was no evidence of differences between either Uva-ursi vs. placebo or ibuprofen advice vs. no advice in terms of symptom severity after 2–4 days (primary outcome). Antibiotic use was a little lower than anticipated from previous studies where 77% of those randomized to a 'delayed prescription' took their antibiotic treatment. In this study (42/74) 56.8% of those in the control arm took antibiotics in the first 2 weeks. While the odds ratios suggest substantial reduction in antibiotic use for both Uva-ursi (0.59; 95% CI 0.22–1.58) and ibuprofen advice (0.27; 95% CI 0.10–0.72) for Uva-ursi the confidence intervals were wide and the results did not reach statistical significance. There were no episodes of upper tract infection and only two serious adverse events.

Strengths and limitations

This is a large study in primary care recruiting women presenting with typical symptoms of urinary tract infection in whom the majority in usual care would usually be treated with antibiotic therapy. Older women were excluded because urinary infection is common but the precise diagnosis becomes less certain, so the results cannot be generalized to an older population. Women who met the existing cautions or contra-indications to ibuprofen (which include asthma) were not included hence limiting the ability to test the Uva-ursi which had no such restrictions in a wider group. The maximum quoted dose of ibuprofen is 2400 mg per day; however, in clinical practice lower doses are usually offered. We used the dose which is commonly recommended and was used for UTIs in previous studies. It is plausible that higher doses may have resulted in more symptom response. Follow-up data were limited, with 248 out of 382 patients (35%) missing some primary endpoint information, hence potentially reducing the internal validity of the trial; however, analysis using all participants and multiple imputation should largely account for this deficiency. Moreover the inferences were unchanged in the per protocol analysis.

Comparison with literature

The confirmed frequency of urine infection (32%) was low compared with previous studies using similar entry criteria but this

Table 3
Analysis of covariance of mean frequency symptom severity score on Days 2–4[a] (ITT population B, $n = 382$)

Characteristic	Statistic			
Primary comparison model (Uva-ursi versus no Uva-ursi − advice to take ibuprofen versus no advice to take ibuprofen)				
Primary endpoints (least squares means)	**Estimate**	**Difference**	**95% CI of LS mean**	**Two-sided p**
Group 1 + 3[b] Uva-ursi ($n = 199$)	1.83	−0.06	(−0.33, 0.21)	0.661
Group 2 + 4[b] Placebo ($n = 183$)	1.89			
Group 1 + 2[b] Ibuprofen advice ($n = 188$)	1.86	−0.01	(−0.27, 0.26)	0.951
Group 3 + 4[b] No advice ($n = 194$)	1.87			
Model coefficients	**Estimate**	**95% CI**		**Two-sided p**
Group 1 + 3[b]	−0.06	(−0.33, 0.21)		0.661
Group 2 + 4[b]	0 (Ref)	—		—
Group 1 + 2[b]	-0.01	(−0.27, 0.26)		0.951
Group 3 + 4[b]	0 (Ref)	—		—
Intercept	0.98	(0.40, 1.57)		<0.001
Frequency symptom severity at baseline	0.41	(0.29, 0.53)		<0.001
Age	0	(−0.01, 0.01)		0.636

The interaction effect between Uva-ursi and ibuprofen was not found to be significant (p 0.803).
CI, confidence interval; ANCOVA, analysis of covariance; LS means, least squares means.
[a] ANCOVA model, frequency mean symptom severity on Days 2–4 = intercept + treatment group + frequency mean symptom severity at baseline + age.
[b] Group 1 + 3, patients who received Uva-ursi; Group 2 + 4, patients who received Uva-ursi placebo; Group 1 + 2, patients who received advice to take ibuprofen; Group 3 + 4, patients who received no advice to take ibuprofen.

Table 4
Analysis of covariance of mean frequency symptom severity score on Days 2–4[a] controlling for antibiotic use (ITT population B, $n = 382$)

Characteristic	Statistic			
Comparison Model (Uva-ursi versus no Uva-ursi − advice to take ibuprofen versus no advice to take ibuprofen, controlling for antibiotic use)				
Least squares means	**Estimate**	**Difference**	**95% CI of LS Mean**	**Two-sided p[a]**
Group 1 + 3[b] Uva-ursi ($n = 199$)	1.92	−0.05	(−0.32, 0.21)	0.704
Group 2 + 4[b] Placebo ($n = 183$)	1.97			
Group 1 + 2[b] Ibuprofen advice ($n = 188$)	1.97	0.04	(−0.24, 0.31)	0.791
Group 3 + 4[b] No advice ($n = 194$)	1.93			
Model coefficients	**Estimate**	**95% CI**		**p**
Group 1 + 3[b]	-0.05	(−0.32, 0.21)		0.704
Group 2 + 4[b]	0 (Ref)	—		—
Group 1 + 2[b]	0.04	(−0.24, 0.31)		0.791
Group 3 + 4[b]	0 (Ref)	—		—
Intercept	0.86	(0.32, 1.41)		0.002
Frequency symptom severity at baseline	0.41	(0.30, 0.53)		<0.001
Antibiotic use up to Day 4 − Yes	0.31	(0.02, 0.60)		0.033
Antibiotic use up to Day 4 − No	0 (Ref)	—		—
Age	0	(−0.01, 0.01)		0.672

The interaction effect between Uva-ursi and ibuprofen was not found to be significant (p 0.782).
CI, confidence interval; ANCOVA, analysis of covariance; LS means, least squares means.
[a] ANCOVA model: Frequency mean symptom severity on Days 2–4, intercept + treatment group + frequency mean symptom severity at baseline + age + antibiotic use up to Day 4.
[b] Group 1 + 3, patients who received Uva-ursi; Group 2 + 4, patients who received Uva-ursi placebo; Group 1 + 2, patients who received advice to take ibuprofen; Group 3 + 4, patients who received no advice to take ibuprofen.

may reflect changes in presentation in primary care in the UK since a more recent study (POETIC) using similar entry criteria showed comparable frequencies [4,14,16,17]. Despite the low frequency of confirmed infection in routine care the majority of women will still receive antibiotics (90%) and so these results are still generalizable to the majority of women presenting [17]. In terms of symptom severity at recruitment, it would be anticipated that those agreeing to participate (and accepting a delayed prescription) might have less severe symptoms; this appears to be the case. In two comparable trials in urine infection the simple sum (SD) of three frequency items (urgency, daytime frequency, and night time frequency) was 9.6 (3.7) (information from authors) [13] and 9.5 respectively [17]. In comparison, in this study the sum of these three frequency items was 7.5 (3.8). The inclusion of women with less severe symptoms may limit the ability of the diary to demonstrate change during recovery although an analysis of those with more severe symptoms still showed no effect on symptoms despite maintaining the effect on antibiotics.

A major concern over withholding of antibiotics is the potential for progressive infection and upper urinary tract infection. All three studies of NSAID in UTI reported an excess of pyelonephritis in the NSAID arm compared with antibiotic [9–11]. In contrast, no episodes of upper tract infection were reported in this study. It is possible that this difference is explained by the design in which all participants were provided with back-up antibiotics and thus those with progressive symptoms had the option for prompt self-management. It is also plausible that the women selected for recruitment in the current study with less severe symptoms at study entry were also at lower risk of subsequent upper tract infection.

Implications for practice

In this study we were able to demonstrate a substantial reduction in antibiotic use compared with usual care with no reported episodes of upper tract infection. We were not able to demonstrate superiority of either intervention over placebo in terms of symptom relief or speed of recovery. Although the results are consistent with reduced antibiotic consumption when active symptom relief is provided (Uva-ursi) or recommended (ibuprofen), this result only

Table 5
Summary of use of antibiotics (ITT population A, $n = 382$)

Characteristic	Group 1[a] (uva-ursi + ibuprofen advice) ($n = 102$)	Group 2[a] (Placebo + Ibuprofen advice) ($n = 86$)	Group 3[a] (uva-ursi + No ibuprofen advice) ($n = 97$)	Group 4[a] (Placebo + No Ibuprofen advice) ($n = 97$)	Group 1+3[b] (uva ursi) ($n = 199$)	Group 2+4[b] (Placebo) ($n = 183$)	Group 1+2[b] (Ibuprofen advice) ($n = 188$)	Group 3+4[b] (No advice) ($n = 194$)	Total ($n = 382$)
Use of antibiotics at any time during Week 1, *n* (%)	17 (24.3)	21 (35.6)	33 (45.2)	41 (55.4)	50 (35.0)	62 (46.6)	38 (29.5)	74 (50.3)	112 (40.6)
Use of antibiotics at any time during Week 1 and Week 2, *n* (%)	24 (34.3)	21 (35.6)	33 (45.2)	42 (56.8)	57 (39.9)	63 (47.4)	45 (34.9)	75 (51.0)	120 (43.5)
Use of antibiotics as recorded in the medical notes review, *n* (%)[c]	21 (77.8)	15 (83.3)	22 (91.7)	23 (85.2)	43 (84.3)	38 (84.4)	36 (80.0)	45 (88.2)	81 (84.4)

[a] Group 1, patients who received Uva-ursi and advice to take ibuprofen; Group 2, patients who received Uva-ursi placebo and advice to take ibuprofen; Group 3, patients who received Uva-ursi and no advice to take ibuprofen; Group 4, patients who received Uva-ursi placebo and no advice to take ibuprofen.
[b] Group 1 + 3, patients who received Uva-ursi; Group 2 + 4, patients who received Uva-ursi placebo; Group 1 + 2, patients who received advice to take ibuprofen; Group 3 + 4, patients who received no advice to take ibuprofen.
[c] This is any re-consultation with urinary tract infection symptoms after the initial consultation as recorded in the 3 month data.

Table 6
Logistic regression model results for use of antibiotics during Week 1 and Week 2 (ITT population A, $n = 382$ (276)[a])

Characteristic	Estimate	SE	Two-sided p
Intercept	0.24	0.47	0.616
Group 1 (Uva-ursi + Ibuprofen)	−0.92	0.34	0.007
Group 2 (Uva-ursi placebo + Ibuprofen)	−0.86	0.36	0.018
Group 3 (Uva-ursi + Ibuprofen placebo)	−0.46	0.33	0.162
Group 4 (Uva-ursi placebo + Ibuprofen placebo)	0 (Ref)	—	—
Age	0.0007	0.01	0.934
Comparison	**Odds ratio**[b]	**95% CI**	**Two-sided p**
Group: 1 + 3 vs. 2 + 4[c] (Uva ursi vs. placebo)	0.59	(0.22 to 1.58)	0.293
Group: 1 + 2 vs. 3 + 4[c] (Ibuprofen advice vs. no advice)	0.27	(0.10 to 0.72)	0.009

SE, standard error; CI, confidence interval.
[a] Population A consist of 382 patients, of which 276 patients had complete information and were included in the logistic regression analysis.
[b] Odds ratios above 1 represent a favourable outcome for the first category in the comparison.
[c] Group 1 + 3, patients who received Uva-ursi; Group 2 + 4, patients who received Uva-ursi placebo; Group 1 + 2, patients who received advice to take ibuprofen; Group 3 + 4, Patients who received no advice to take ibuprofen.

Table 7
Re-consultation with urinary tract infection − from diary data (ITT population A, $n = 382$)

	Group 1[a] (Uva-ursi + ibuprofen advice) ($n = 102$)	Group 2[a] Placebo + Ibuprofen advice ($n = 86$)	Group 3[a] Uva-ursi + No ibuprofen advice ($n = 97$)	Group 4[a] Placebo + No Ibuprofen advice ($n = 97$)	Total ($n = 382$)
Re-consultation with symptoms of UTI within one month as recorded in the three month medical notes review, *n* (%)	15 (14.7)	11 (12.8)	16 (16.5)	16 (16.5)	58 (15.2)
Re-consultation with symptoms of UTI within three months as recorded in the three month medical notes review, *n* (%)	23 (22.5)	16 (18.6)	22 (22.7)	27 (27.8)	88 (23.0)

[a] Group 1, patients who received Uva-ursi and advice to take ibuprofen; Group 2, patients who received Uva-ursi placebo and advice to take ibuprofen; Group 3, patients who received Uva-ursi and no advice to take ibuprofen; Group 4, patients who received Uva-ursi placebo and no advice to take ibuprofen.

reached statistical significance for ibuprofen. Use of a delayed prescription in tandem with advice to take ibuprofen is a good option for women with *less severe* urinary symptoms and *willing to delay* antibiotic use based on current evidence and is likely to result in substantial reduction in antibiotic use compared to usual care.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. This paper presents independent research funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR). The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health. All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations including industry that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. This project is funded by the National Institute for Health Research (NIHR) School of Primary Care, project number 170. The project is sponsored by the University of Southampton. Relevant anonymized patient level data available after approval of the proposal and with a data sharing agreement. The study protocol has been published. Statistical analysis plan and consent form will be published on the institution repository.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.01.011.

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