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Original article

Herbal treatment with uva ursi extract versus fosfomycin in women with uncomplicated urinary tract infection in primary care: a randomized controlled trial

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ABSTRACT

Objective: We explored whether initial treatment with the herbal drug uva ursi (UU) reduces antibiotic use in women with uncomplicated urinary tract infection (UTI) without increasing symptom burden and complication frequency compared with antibiotic treatment.
Methods: A double-blind randomized controlled trial was conducted in 42 family practices in Germany. The participants were adult women with suspected uncomplicated UTIs receiving either UU 105 mg 3 × 2 tablets for 5 days (intervention) or fosfomycin a 3-g single dose (control), and their respective placebos. Participants and investigators were blinded. The primary outcome included (1) antibiotic courses day 0–28 as superiority, and (2) symptom burden (sum of daily symptom scores) day 0–7, as non-inferiority outcome (margin 125%). Clinicaltrials.gov: NCT03151603.
Results: Overall, 398 patients were randomly allocated to groups receiving UU ($n = 207$) and fosfomycin ($n = 191$). The number of antibiotic courses was 63.6% lower (95% CI 53.6%–71.4%; $p < 0.0001$) in the UU group than in the fosfomycin group. The ratio of total symptom burden in the UU group compared with control was 136.5% (95% CI 122.7–151.9; p 0.95), failing non-inferiority. Eight women developed pyelonephritis in the UU group compared with two in the fosfomycin group (mean difference 2.8; 95% CI 0.2–5.9; p 0.067). Adverse events were similar between the groups.
Discussion: In women with uncomplicated UTIs, initial treatment with UU reduced antibiotic use but led to a higher symptom burden and more safety concerns than fosfomycin. **Ildikó Gágyor, Clin Microbiol Infect 2021;27:1441**

Introduction

Uncomplicated urinary tract infections (UTIs) warrant a substantial share of antibiotic prescriptions in primary care [1–3], thereby contributing to increasing resistance rates [4] in an era of limited antibiotic choices.

Herbal remedies are potential treatments for bacterial infections [5]. They possess antibacterial properties [6]; however, their role as alternatives to antibiotics in uncomplicated UTI has not been comprehensively studied. Uva ursi (UU), a herbal drug, has traditionally been used to treat UTI symptoms [1,7,8] despite limited evidence of its effectiveness and safety [9,10]. Its antiseptic and antimicrobial effects have been attributed to hydroquinones and tannins [11].

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The only trial conducted on UU as an add-on to delayed prescription revealed no effect on the severity and frequency of symptoms; however, delayed prescription of antibiotics was used in all groups and UU has not been directly compared with antibiotics [9]. This study determines whether initial treatment with UU is superior to fosfomycin in terms of reducing antibiotic use in women with uncomplicated UTI, and non-inferior in terms of increasing symptom burden or complication frequency (margin 125%).

Materials and methods

Study design, setting, and participants

REGATTA (reducing antibiotic use for uncomplicated UTI in general practice by treatment with UU) was a pragmatic double-blind, double-dummy, randomized controlled trial with two groups conducted in 42 family practices in Germany. Women diagnosed with uncomplicated UTI were assessed for eligibility and enrolled by family physicians (FPs) [12]. Inclusion criteria were age 18–75 years and at least two of the following symptoms: dysuria, urgency, frequency and lower abdominal pain. Exclusion criteria were signs of and risks factors for complicated UTI like fever or pregnancy (details in Afshar et al. [13]). Recruitment started on 3 May 2017 and ended on 23 May 2019. Safety follow-up was completed in August 2019.

The trial was performed according to the Good Clinical Practice guidelines, Declaration of Helsinki, and followed the SPIRIT guidelines [14]. REGATTA was approved by the local ethics committee (ref. no. 16/11/16). All participants gave informed consent.

Randomization and masking

Participants were randomly assigned to receive UU (105 mg arbutin, 3 × 2 tablets daily) for 5 days, or fosfomycin powder (3 g) as a single dose or respective placebos. Computerized randomization was performed by the trial statistician at patient level, with block lengths of 2–6 at a ratio of 1:1. Random sequence generation numbers and sample size calculation were obtained using nQuery Advisor 4.0 [15]. Allocation was stratified according to trial site. Sealed opaque envelopes were stored for each practice, and a randomization list was maintained in the trial pharmacy to unblind patients in case of an emergency. The trial statistician did not recruit patients or collect data. Participants, FPs and study team were blinded.

Procedures

The trial pharmacy transferred fosfomycin and placebo granules to bottles. To produce a solution of uniform taste, a box of orange juice was added to the fosfomycin and respective placebo granules before consumption. For more details see Afshar et al. [13].

Participants provided urine samples for dipstick, urine culture and pregnancy tests, and had their temperature recorded. The trial protocol provided for one urine culture at inclusion. Results were considered positive in presence of $\geq 10^3$ CFU/ml. Participants completed a validated eight-item symptom questionnaire (UTI-SIQ-8) to assess symptom severity and UTI-related activity impairment due to each symptom [16]. Each item was scored from 0 (none) to 4 (very strong).Duration of symptoms, previous UTI episodes, comorbidity, medication and sociodemographic data were collected at baseline. Participants were instructed to re-consult if persistent, worsening or recurrent UTI symptoms or fever occurred. Antibiotic treatment recommended in the UTI guidelines was then initiated at the FP's discretion [17].

Participants completed a symptom diary for at least 7 days until symptom resolution (maximum one point on each symptom scale). The diary comprised the UTI-SIQ-8 questionnaire and additional questions on analgesics and any antibiotic treatment. Participants were followed up until symptom resolution (maximum of 1 point on each symptom scale). On day 28, they returned diaries and empty trial drug packages, and completed a final questionnaire on antibiotic intake, relapsed and recurrent UTI, adverse events (AEs), serious AEs (SAEs), UTI-related consultations and days of sick leave. After 3 months, participants were asked by phone whether they had experienced recurrent UTI or pyelonephritis.

Outcomes

The two primary outcomes were the number of all antibiotic courses, regardless of their medical indication from day 0 to 28, and symptom burden, defined as the weighted sum of the total daily symptom scores from day 0 to 7, measured as the area under the curve (AUC) of the total daily symptom score [18–20]. If the initial treatment with UU was superior considering the number of antibiotic courses, one of the primary outcomes, and non-inferior considering the other primary outcome, namely the symptom burden (non-inferiority margin 125%), the trial result was deemed positive.

Secondary outcomes were the number of early relapses (occurrence of UTI symptoms on days 0–14), number of recurrent UTI events (occurrence of UTI on days 15–28), number of patients with symptom resolution by days 4 and 7, symptom burden for individual symptoms stratified by positive or negative urine culture results on days 0–7, activity impairment due to UTI symptoms on days 0–7, use of analgesics (defined daily doses (DDDs)) on days 0–7, number of patients taking analgesics on days 0–7, use of antibiotics (DDD), number of UTI-related consultations on days 0–28 and number of days of UTI-related sick leave (days 0–28). For safety outcome measures please see supplementary material.

Statistical analysis

We assumed that the coefficient of variation of symptom burden was 70% [18]. The sample size required to demonstrate non-inferiority (i.e. the symptom burden of the UU group being lower than 125% of that of the fosfomycin group) at a one-sided significance level of 2.5% with a power of 90% was 170 patients per group. We aimed to randomize 430 patients (expected dropout rate 20%). The sample size was also sufficient for the primary endpoint, the number of antibiotic courses [13]. In May 2019, the shelf time of the trial drugs expired, and recruitment was closed with 398 patients.

In the intention to treat analysis, multiple imputation techniques were used to deal with missing values. The primary analysis was based on (1) the rate of antibiotic courses per patient within days 0–28 in the UU group being greater or equal to (H0) or lower (H1) than that in the fosfomycin group and (2) the symptom burden within 0–7 days in the UU group was greater than or equal to (H0) or lower than (H1) 125% of that in the fosfomycin group. Both hypotheses were tested at a one-sided level of 2.5%.

The number of antibiotic courses within 0–28 days was compared between the groups using Wilcoxon rank sum test. The intervention effect is described as a rate ratio (with 95% CI), resulting from a negative binomial regression adjusted for centre and baseline symptom scores. An analysis of covariance of the logarithm of the symptom burden was performed with the treatment group as factor and day 0 (inclusion) logarithm of the sum of symptom scores as a covariate. From this model, the upper limit of the two-sided 95% CI for the ratio of the expected total symptom burden of initial UU use versus immediate antibiotic use was

derived and compared to the non-inferiority margin of 125%, which is an established margin in other applications such as bioequivalence trials [18,21].

An independent data and safety monitoring board assessed the safety outcomes during the trial. The trial is registered with EudraCT as 2016–000477–21 and Clinical trials.gov as NCT03151603.

Results

Participants

Recruitment and patient flow are presented in Fig. 1. For patient characteristics and baseline data (Table 1). Trial participants had more severe UTI symptoms than non-participants (see Table S5).

Outcomes

The number of all antibiotic courses from days 0–28 was reduced by 63.6% in the UU group, with 92 antibiotic courses (82 for UTI and 10 for other reasons) compared with 233 antibiotic courses in the fosfomycin group (189 for treating UTI as a part of the study protocol plus 44 courses prescribed additionally, including 34 for UTI and 10 for other reasons). This was confirmed in a negative binomial regression analysis with a rate ratio of 0.38 (95% CI 0.30–0.49; $p < 0.0001$), corresponding to a 62% reduction (Table 2).

The total symptom burden decreased more slowly in the UU group than in the fosfomycin group, resulting in a ratio of 136.5% (95% CI 122.7–151.9%; p 0.95) from days 0 to 7 (Fig. 2).

The results in the PP population were similar, with 134.1% (95% CI 119.8–150.1%; p 0.89) (Fig. S1). Thus, the non-inferiority margin of 125% was exceeded, and the hypothesis of non-inferiority must be rejected. Symptom burden for each UTI symptom from days 0 to 7 showed similar patterns (Table S2). Women with positive urine cultures benefited more from antibiotic treatment than from UU, but no difference was observed in women with negative urine cultures between the groups (Table 2, Fig. S2). The mean duration of UTI symptoms was 4.2 days and 3.4 days in the UU and fosfomycin groups, respectively (difference 0.8 days; 95% CI 0.3–13; p 0.0008), verified as the time to symptom resolution using the Kaplan–Meier estimator (Fig. S3).

On day 4, the number of women with symptom resolution was significantly lower in the UU group (101 (48.8%) vs. 125 (65.4%); mean difference −16.7; 95% CI −26.2 to −7.1; $p < 0.0004$]) than in the fosfomycin group. Relapses until day 14 were less frequent in the UU group, whereas recurrent UTI on days 15–28 and after day 28 were more common (Table 2). These results were not significant, and no difference was observed in the sensitivity analyses between those with and without a history of recurrent UTI (Table S6).

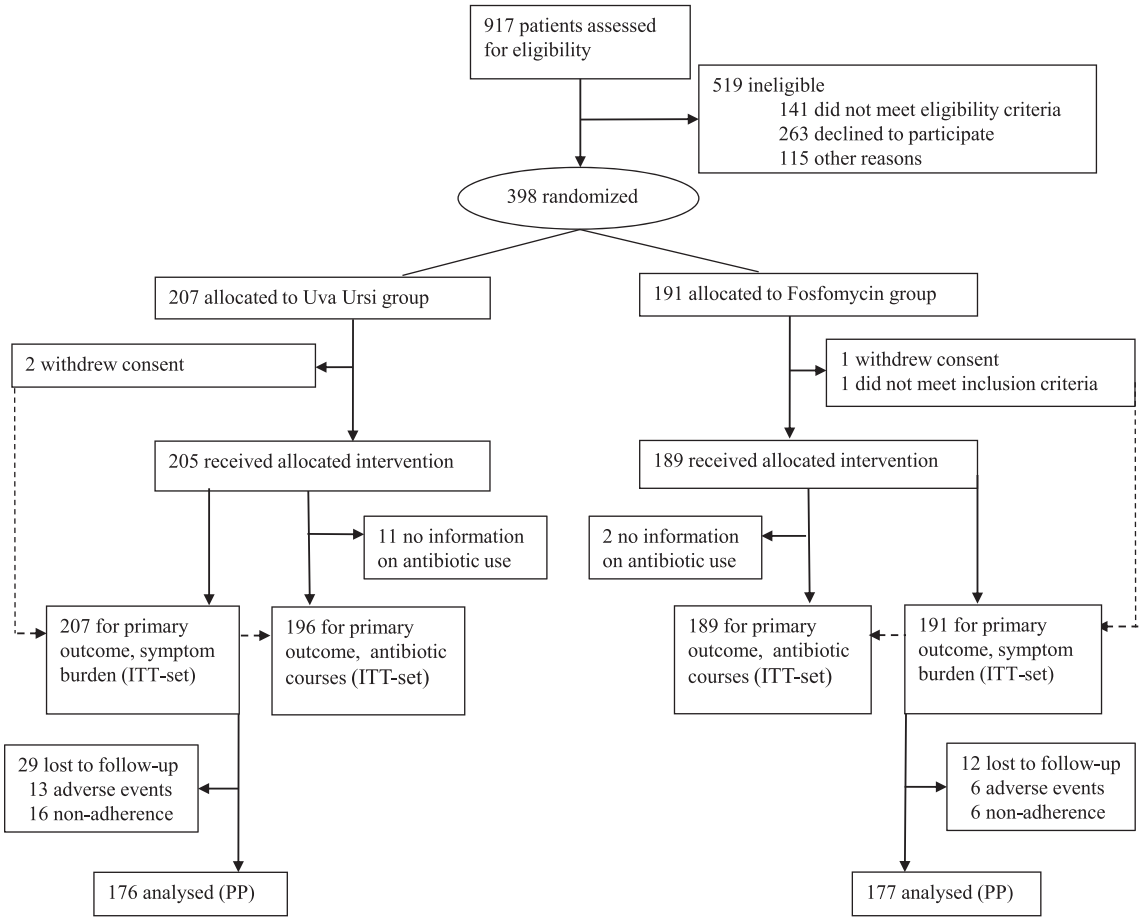

Fig. 1. Trial profile. Eligible women were allocated at a ratio of 1:1 to receive either UU (105 mg arbutin, 3 × 2 daily) for 5 days, or fosfomycin powder (3 g) as a single dose or the respective placebos. Of these, four did not take the study medication post randomization. Thirteen women were excluded from the primary outcome analysis for antibiotic use, as no information was available on antibiotic intake. All randomized patients were analysed for the primary outcome, symptom burden. The PP analysis included 353 patients. PP, per protocol; ITT, intention to treat.

Table 1
Baseline characteristics

	Uva ursi ($n = 207$)	Fosfomycin ($n = 191$)	Total ($n = 398$)
Age (years), Mean (SD)	41.9 (15.1)[a]	46.8 (17.1)	44.2 (16.3)
Duration of symptoms at inclusion (d)			
Mean (SD)	5.3 (11.3)[a]	5.3 (8.8)[b]	5.3 (10.2)
Median (IQR)	2.0 (2.0 to 5.0)	3.0 (2.0 to 6.0)	3.0 (2.0 to 5.0)
Symptoms at inclusion, *n* (%)			
Dysuria	179 (86.5)	166 (87.4)[a]	345 (86.9)
Urgent urination	183 (88.4)	176 (92.6)	359 (90.4)
Frequent urination	181 (87.4)	172 (90.5)	353 (88.9)
Lower abdominal pain	134 (64.7)	113 (59.5)	247 (62.2)
Symptom sum score (0–16), mean (SD)	9.0 (2.9)[c]	9.4 (2.8)[d]	9.2 (2.8)
Dysuria subscore (0–4)	2.5 (0.8)	2.7 (0.8)	2.6 (0.8)
Urgency of urination subscore (0–4)	2.3 (1.1)	2.3 (1.2)	2.3 (1.1)
Frequency of urination subscore (0–4)	2.5 (1.0)	2.6 (0.9)	2.6 (0.9)
Lower abdominal pain subscore (0–4)	1.7 (1.2)	1.8 (1.2)	1.7 (1.2)
Activity impairment sum score (0–16)	8.3 (3.2)	8.4 (3.1)	8.4 (3.1)
Recurrent UTI (within last 6 months), *n* (%)	72 (35.1)[e]	56 (29.9)[f]	128 (32.7)
Dipstick results, *n* (%)			
Leucocyte positive	170 (82.5)[a]	158 (83.6)[g]	328 (83.0)
Erythrocyte positive	162 (78.6)	146 (77.7)	308 (78.2)
Nitrite positive	41 (19.9)	40 (21.3)	81 (20.6)
Culture results, *n* (%)			
Positive	173 (86.9)[h]	154 (83.2)[i]	327 (85.2
Escherichia coli	142 (82.1)	130 (84.4)	272 (83.2)
Susceptibility to fosfomycin	140 (98.6)	130 (100.0)	270 (99.3)

UTI, urinary tract infection; SD, standard deviation; IQR, interquartile range.
[a] One value missing.
[b] Six questionnaires not available.
[c] Up to two values missing.
[d] Up to six values missing.
[e] Two values missing.
[f] Four values missing.
[g] Three values missing.
[h] Eight cultures were not tested or contaminated.
[i] Six cultures were not tested or contaminated.

The use of analgesics on days 0–28 was significantly higher in the UU group (0.09 vs. 0.04 DDD per patient; difference 0.05; 95% CI 0.02–0.08; p 0.0017) (Fig. 3). Moreover, the mean number of consultations in the UU group was higher (Table 2).

Safety

Pyelonephritis and fever were more common in the UU group (eight patients with pyelonephritis vs. two and three patients with fever vs. none). The number of women with worsening symptoms was higher in the UU group (16 UU and 10 fosfomycin), and the same was true for prolonged symptoms (17 UU and 12 fosfomycin) (Table S3). These results were not statistically significant.

AEs occurred equally in both groups. At least one AE was reported in 82 (40.0%) and 82 (43.4%) women in the UU and fosfomycin groups, respectively (Table S4). Four SAEs not related to UTI (pneumonia, ankle fracture, atrial fibrillation, and diarrhoea) occurred and required treatment. Causality to the trial drugs was assessed as unlikely. Four women with pyelonephritis were treated in the hospital and recovered fully.

Discussion

In this trial, initial treatment with UU reduced the overall number of antibiotic treatment courses taken by women with uncomplicated UTI. However, this resulted in a higher symptom burden with an AUC ratio of 136.5% and more cases of pyelonephritis or fever. Therefore, the assumption of non-inferiority of initial treatment with UU must be rejected. Furthermore, women in the UU group recovered more slowly, consumed more analgesics, re-consulted more often, and took more sick leave.

The overall reduction in antibiotic use is not surprising, as the study design included the control group trial drug in the primary outcome to assess whether antibiotic exposure is reduced. We included the control (fosfomycin) in the outcome (antibiotic use for days 0–28) to determine whether the overall antibiotic exposure was reduced when treating with UU first. Importantly, when excluding the trial drug fosfomycin, the subsequent antibiotic use was higher in the UU group (23% vs. 44%). However, the overall exposition to antibiotics was higher in the fosfomycin group which is more relevant from the antimicrobial stewardship perspective.

Our results corroborate the findings of similar trials. In our UU group, 61% of the participants recovered without antibiotics, which is comparable with previous evidence. RCTs with placebo groups indicate that 28–54% of uncomplicated UTI cases are self-limiting [9,22,23]. These results, however, should be interpreted with caution, because the design of these trials did not permit to reliably assess the effectiveness of placebo (e.g. due to factorial design, patients lost to follow up).

Trials assessing treatment with non-steroidal anti-inflammatory drugs and antibiotics consistently showed a reduction in antibiotic use. This was demonstrated in the ICUTI trial, where 65% of the women in the ibuprofen group recovered without antibiotics within a week [18]. The proportion of recovered women was lower in the trial by Vik et al., with 39% on day 4 and 53% at 4 weeks after inclusion in 181 patients [24]. Kronenberg et al. reported a 54% reduction in antibiotics by day 3 in 133 women treated with diclofenac [25]. When testing advice to take ibuprofen and UU in a factorial design, 66% of the women treated with UU plus ibuprofen if needed and 55% of women treated with only UU recovered without taking antibiotics [9]. Therefore, combining both treatments may be more effective than one

Table 2
Antibiotic courses, symptom burden and other health outcomes (intention to treat population)

	Uva Ursi (n = 207)	Fosfomycin (n = 191)	Intervention effect (ratio for antibiotic courses, otherwise mean difference) (95% CI)	p value
Number of antibiotic courses per patient, days 0–28, Mean (SD)	0.44 (0.62)	1.22 (0.54)	0.38 (0.30 to 0.49)	<0.0001
Total[a], *n* (%)	92 (44.4)	233 (121.9)		
During follow-up, *n* (%)	92 (44.4)	44 (23.0)		
During follow-up (due to UTI), *n* (%)	82 (39.6)	34 (17.8)		
Women receiving antibiotics on days 0–28, *n* (%)				<0.0001
Total[a]	80 (38.6)	189 (99.0)	−60.3 (−67.1 to −53.5)	
During follow-up (total)	80 (38.6)	36 (18.8)	19.8 (11.2 to 28.5)	
During follow-up (due to UTI)	72 (34.8)	28 (14.7)	20.1 (11.9 to 28.3)	
Symptom burden[b,d,e,f] on days 0–7, Mean (SE)	36.2 (1.1)	27.1 (1.1)	9.1 (5.9 to 12.2)	0.95[c]
Symptom burden[b,c,d,e,f] on days 0–7, Mean (SE)	34.7 (1.1)	26.1 (1.2)	8.5 (5.3 to 11.8)	0.89[c]
Symptom burden[b,d], Mean (SE)				<0 .0001
Patients with positive urine culture	38.0 (1.2)	26.0 (1.2)	11.9 (8.5 to 15.3)	
Patients with negative urine culture	23.1 (3.1)	29.9 (2.9)	−6.8 (−15.2 to 1.5)	0.11
Early relapse (days 0–14), *n* (%)	14 (6.8)	20 (10.5)	−3.7 (−9.2 to 1.8)	0.14
Recurrent UTI occurring on days 15–28, *n* (%)	20 (9.7)	13 (6.8)	2.9 (−2.5 to 8.2)	0.44
Recurrent UTI occurring from day 29 to 3 months [g]	31 (17)	22 (12)	4.7 (−2.6 to 12.0)	0.21
Activity impairment by UTI symptoms, mean (SE)[b,c,d,e,f]	32.2 (1.1)	23.4 (1.2)	8.8 (5.6 to 12.0)	<0.0001
Patients taking analgesics, n (%)	88 (42.5)	59 (30.9)	−11.6 (−21.0 to −2.2)	0.013
Use of analgesics (DDDs/day and patient) on days 0–7, mean (SD)	0.087 (0.186)	0.041 (0.095)	0.046 (0.017 to 0.075)	0.0017
Use of antibiotics (DDDs/day and patient) on days 0–28, mean (SD)	0.088 (0.219)	0.069 (0.090)	0.019 (−0.014 −to 0.051)	0.26
UTI-related consultations on days 0–28, mean (SD)	0.46 (0.64)	0.22 (0.57)	0.24 (0.12 to 0.36)	<0.0001
UTI-related days for sick leave from days 0–28, mean (SD)[h]	0.95 (2.42)	0.46 (1.91)	0.49 (0.05 to 0.94)	0.029

AUC, area under the curve; UTI, urinary tract infection; DDD, defined daily doses; SD, standard deviation; SE, standard error.
[a] Includes control (fosfomycin).
[b] Defined as AUC of daily symptom sum score from days 0 to 7.
[c] Defined as area under the curve (AUC) of daily activity impairment scores based on UTI symptoms from days 0 to 7.
[d] Per protocol population.
[e] Test for non-inferiority of uva ursi versus fosfomycin (margin: 125%).
[f] According to multiple imputation and after fitting a statistical model: least square means.
[g] 182 completed questionnaires in the Uva Ursi group and 178 in the fosfomycin group.
[h] Sensitivity analysis.

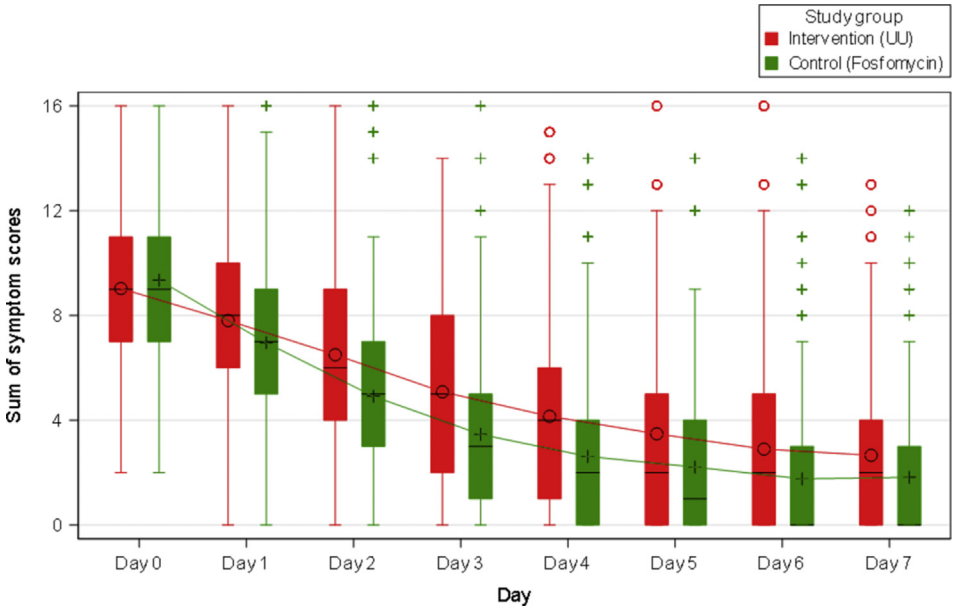

Fig. 2. Symptom burden, primary outcome, and intention-to-treat population. Symptom burden (AUC) ratio as the weighted sum of symptom scores on days 0–7 (0–16): 136.5% (95% CI 122.7%–151.9%, p 0.92). The whiskers range between the first and third quartiles (−1.5 to +1.5 IQR). The box ranges between the first and third quartiles. The line and the cross/circle within the box represent the median and mean, respectively. Outliers are indicated. AUC, area under the curve; IQR, interquartile range.

treatment alone. The higher consumption of analgesics in the UU group in our trial indicates the same. However, comparability is limited, as the ATAFUTI population had less severe symptoms and a low proportion of bacteriologically confirmed UTI (32%) [9]. The highest reduction rates were observed in a trial with a herbal drug (BNO 1045), where 83.5% of the patients in the intervention group did not take antibiotics during the 38-day follow-up period [26]. A meta-analysis comparing these trials

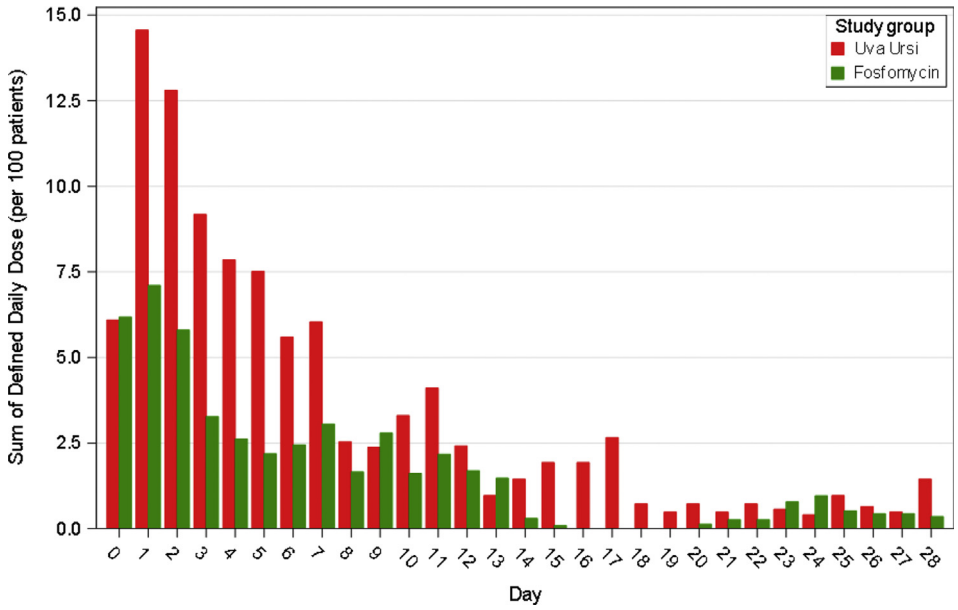

Fig. 3. Use of analgesics on days 0–28 in the intention-to-treat population. Sum of DDD; Analgesics taken: ibuprofen, paracetamol, acetylsalicylic acid, diclofenac, naproxen, metamizole, and others. The use of analgesics from days 0 to 7 was 0.09 versus 0.04 DDD per patient; MD: 0.05 (95% CI 0.02–0.08). Proportions of analgesics on days 0–28 (DDD): ibuprofen (85.87%), paracetamol (4.00%), acetylsalicylic acid (1.39%), diclofenac (2.15%), naproxen (1.67%), metamizole (0.22%), and others (4.71%). Frequencies of analgesics without taking into account the daily dose per person on days 0-28: ibuprofen (378), paracetamol (44), acetylsalicylic acid (12), diclofenac (10), naproxen (3), metamizole (29) and others (23). DDD, defined daily doses; MD, mean difference.

is in progress aiming to identify who may benefit from alternative approaches to reduce antibiotic use and those susceptible to adverse outcomes [27].

We chose fosfomycin because it is a first-line treatment in Germany and several other countries [17,28,29]. However, in a previous trial, fosfomycin proved less effective than nitrofurantoin, which may explain the 23% additional antibiotics in the fosfomycin group [30].

Although the overall number of AEs was similar in both groups, UU was less safe according to the safety outcomes. In previous trials in the antibiotic groups, 0–1% of the participants developed pyelonephritis or fever compared with 1.8–5.3% in the intervention groups [18,24,25]. A meta-analysis of trials comparing placebo with antibiotics reported an incidence of pyelonephritis ranging from 0.4% to 2.6% [31]. No relevant complications were reported in trials supplying a delayed prescription of a back-up antibiotic [9,32].

In our ICUTI [18] trial, more recurrent UTIs occurred in the antibiotic group, whereas REGATTA showed more recurrent infections after day 14 in the UU group (not significant). For this outcome, the sensitivity analysis did not reveal a difference between women with and without a history of recurrent UTI [9,24,25].

This trial has some limitations. Randomization resulted in some imbalance in the group size and some baseline characteristics. The sensitivity analyses concerning the imbalances in the baseline characteristics (adaptive regression) indicated no relevant effect on the symptom burden. The loss to follow-up rate was 11.3% with more women in the UU group. This could be explained by the UU group's higher symptom burden.

Approximately 51% of all the women with UTI symptoms could be enrolled in REGATTA. In contrast to the ICUTI trial, participants in REGATTA had more severe UTI symptoms than non-participants. We followed a pragmatic study design by comparing two treatment strategies instead of two drugs, including women with symptoms suggestive of a UTI, and leaving the treatment decision of participants with worsening symptoms to FPs based on guidelines.

These strengths ensure high external validity. Another strength is the high rate of positive urine cultures, 85% compared with 24–77% in similar trials, which may also explain the relatively high rate of pyelonephritis [9,18,24,26]. The proportion of positive nitrite results in REGATTA appears small but similar values have been reported in other clinical trials in primary care (14–21%) [18,24,25].

Our trial confirms that UU potentially reduces antibiotic use, but results in a higher symptom burden, higher rate of pyelonephritis and fever, and prolonged or worsening symptoms. This restricts the use of UU as an initial treatment.

Transparency declaration

All authors declare that they have no competing interests and no financial relationships with any organizations that might have an interest in the submitted work. The present study was funded by the German Federal Ministry of Education and Research (BMBF) No 01KG1601. The funder had no role in the trial design, data collection, data interpretation or report preparation. The corresponding author had full access to all the data in this study and had final responsibility for the decision to submit the manuscript for publication.

Author contributions

I.G., E.H., J.B., G.S. and T.F. contributed to the conception and design of the study. I.G., E.H. and J.B. drafted the manuscript. IG and EH share the first authorship. I.G., E.H. and G.S. acted as investigators and contributed to patient recruitment. I.G., J.B. and K.A. coordinated the study at the regional level. T.F. and S.P. take responsibility for the accuracy of the statistical analyses. I.G. and E.H. are the guarantors of this paper. All authors meet the criteria for authorship.

Access to data

The following individual participant data will be shared on reasonable request to the corresponding author at gagyor_i@ukw.de from the date of publication: anonymized patient data and informed consent form.

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Appendix A. Supplementary data

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