Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial

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ABSTRACT

OBJECTIVE

To investigate whether symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is non-inferior to antibiotics in the treatment of uncomplicated lower urinary tract infection (UTI) in women, thus offering an opportunity to reduce antibiotic use in ambulatory care.

DESIGN

Randomised, double blind, non-inferiority trial.

SETTING

17 general practices in Switzerland.

PARTICIPANTS

253 women with uncomplicated lower UTI were randomly assigned 1:1 to symptomatic treatment with the NSAID diclofenac (n=133) or antibiotic treatment with norfloxacin (n=120). The randomisation sequence was computer generated, stratified by practice, blocked, and concealed using sealed, sequentially numbered drug containers.

MAIN OUTCOME MEASURES

The primary outcome was resolution of symptoms at day 3 (72 hours after randomisation and 12 hours after intake of the last study drug). The prespecified principal secondary outcome was the use of any antibiotic (including norfloxacin and fosfomycin as trial drugs) up to day 30. Analysis was by intention to treat.

RESULTS

72/133 (54%) women assigned to diclofenac and 96/120 (80%) assigned to norfloxacin experienced symptom resolution at day 3 (risk difference 27%, 95% confidence interval 15% to 38%, P=0.98 for non-inferiority, P<0.001 for superiority). The median time until resolution of symptoms was four days in the diclofenac group and two days in the norfloxacin group. A total of 82 (62%) women in the diclofenac group and 118 (98%) in the norfloxacin group used antibiotics up to day 30 (risk difference 37%, 28% to 46%, P<0.001 for superiority). Six women in the diclofenac group (5%) but none in the norfloxacin group received a clinical diagnosis of pyelonephritis (P=0.03).

CONCLUSION

Diclofenac is inferior to norfloxacin for symptom relief of UTI and is likely to be associated with an increased risk of pyelonephritis, even though it reduces antibiotic use in women with uncomplicated lower UTI.

TRIAL REGISTRATION

ClinicalTrials.gov NCT01039545.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Uncomplicated urinary tract infection is a common reason for antibiotic prescription in ambulatory care even though it is often benign and self limiting

Reducing antibiotic usage is important to combat increasing rates of antibiotic resistance

WHAT THIS STUDY ADDS

Symptomatic treatment of lower urinary tract infections prolongs symptom duration and is likely to be associated with an increased risk of pyelonephritis

Introduction

Antimicrobial stewardship aims at reducing antibiotic resistance by optimising or decreasing antibiotic use,[1] which includes the prevention of antibiotic treatment in cases of viral infections, tailored prescription of narrow spectrum antibiotics, shortening the course of treatment, and deferring treatment for low risk bacterial infections. Urinary tract infection (UTI) is one of the most common bacterial infections in adults, affecting considerably more women than men.[2] Approximately half of women have at least one UTI in their lifetime, and 20-30% have two or more.[3] Antibiotic prescriptions for UTI account for 10-20% of all antibiotic prescriptions in ambulatory care and are second only to antibiotic prescriptions for respiratory tract infections.[4 5] Reducing antibiotic prescriptions for UTI could potentially decrease the risk of antibiotic resistance. Therefore, the benefit of antibiotic treatment needs to be weighed against the potential for adverse effects, at both the individual level (adverse drug reactions) and the population level (as a driver of antibiotic resistance).

Symptoms of UTI may arise from local increases in pro-inflammatory factors such as prostaglandins, and non-steroidal anti-inflammatory drugs (NSAIDs) may be useful in alleviating symptoms.[6-8] A small randomised pilot trial, which compared the NSAID ibuprofen with the antibiotic ciprofloxacin in 80 women with uncomplicated lower UTI, concluded that symptomatic treatment with NSAIDs may be non-inferior to antibiotics, but suggested confirmation in a larger trial.[9] Two adequately powered randomised double blind trials were therefore initiated simultaneously in February 2012 in Germany and Switzerland. Results of the German trial, which compared ibuprofen with fosfomycin in 494 women, were recently published.[10] Here we report results

of the Swiss trial, which compared diclofenac with norfloxacin in women with uncomplicated lower UTI.

Methods

Study design

This randomised controlled trial with blinding of patients and assessors was conducted in 17 general practices in the German speaking part of Switzerland. All women provided written informed consent.

Patients, randomisation, and treatment

Women aged 18 to 70 years, who visited their general practitioner because of one or more symptoms or signs typical of acute lower UTI (dysuria, frequency, macrohaematuria, cloudy or smelly urine) or self diagnosed symptomatic cystitis were eligible if their urine dipstick was positive for nitrite or leucocytes, or both. We excluded pregnant women and women with clinical signs of upper UTI such as fever (axillary body temperature >38°C), costovertebral pain or tenderness, rigors, and nausea or vomiting. We also excluded women with known or suspected anatomical or functional abnormality of the urinary tract and comorbidities such as diabetes mellitus, active gastric or duodenal ulcer disease or gastrointestinal bleeding, inflammatory bowel disease, severe liver dysfunction (liver cirrhosis and ascites), coagulopathy (including treatment with coumarine derivates), renal insufficiency grade 3 or higher (calculated glomerular filtration rate <60 mL/min), known congestive heart failure (New York Heart Association (NYHA) III or higher), psychiatric illness or dementia, inability to communicate in German or French, and any other serious comorbidity as judged by the treating doctor. In addition we excluded women with documented immunosuppression (eg, prednisone equivalent >10 mg/day for >14 days, chemotherapy, radiotherapy, immunomodulators, HIV infection, neutropenia) or hypersensitivity to one of the study drugs or a history of asthma, urticaria, or hypersensitivity-like reactions after consumption of salicylic acid or other non-steroidal anti-inflammatory drugs, as well as women with vaginal symptoms (discharge, irritation), bladder catheter in situ or during the past 30 days, recurrent UTI (more than three infections during the past 12 months), antibiotic treatment during the past four weeks, or UTI symptoms present for more than seven days before visiting the doctor.

Women were randomly allocated in a 1:1 ratio to diclofenac or norfloxacin treatment. The randomisation sequence was computer generated, stratified by practice, and blocked with randomly varying block sizes of 4 and 6. Allocation was concealed with sealed, sequentially numbered opaque drug containers of identical appearance that contained opaque hard gelatine capsules of identical size and colour. Women allocated to diclofenac received capsules containing 75 mg diclofenac retard for three days (Olfen-75 duo release; Mepha Pharma, Basel, Switzerland) and women allocated to norfloxacin received capsules containing 400 mg norfloxacin for three days (Norfloxacin-Teva; Teva Pharma, Tel Aviv, Israel; or Norflocin-Mepha; Lactab, Mepha Pharma, Basel, Switzerland from October 2013 onwards owing to delivery restrictions). We chose norfloxacin because of the high susceptibility rates in Switzerland and diclofenac because of its identical frequency of being administered, which facilitated patient blinding. Women started treatment immediately after randomisation on day 0 and were advised to take two capsules each day: one in the morning and one in the evening. All women were given a single open label package of fosfomycin (Monuril; Zambon, Cadempino, Switzerland) to be taken as rescue antibiotic (3 g dose) after completion of the study drug on day 3 at their discretion, if symptoms persisted.

Procedures and outcomes

The prespecified primary outcome was symptom resolution on day 3 (72 hours after randomisation and 12 hours after intake of the last study drug). In the absence of antimicrobial resistance, the mean duration of symptoms in women with uncomplicated UTIs treated with antibiotics is three days.[11] The self report questionnaire used to ascertain severity of symptoms was developed based on questionnaires described by Clayson et al[12] and Little et al.[13] Women rated the severity of five UTI symptoms (dysuria, frequency, urgency, abdominal pain when passing urine, pain or tenderness in the lower back or loin) daily from days 0 (randomisation) to 10 in a diary and on day 30 by telephone interview on a Likert scale from 0 to 6, with their composite score ranging from 0 to 30. Symptom resolution was defined as 2 or less points (slight, very slight, or no problems) on all five components.[12 14 15] Complete absence of symptoms was defined as 0 points on all components. When the trial was registered on ClinicalTrials.gov (NCT01039545), the day of randomisation was defined as day 1, but for the purposes of this report it was defined as day 0. Therefore day 4, described as the time point of the primary outcome on ClinicalTrials.gov, corresponds to day 3 in this report. The prespecified principal secondary outcome was the use of any antibiotic (including norfloxacin and fosfomycin as trial drugs) up to day 30. The remaining prespecified outcomes were resolution of symptoms on day 7; complete absence of symptoms on days 3 and 7; use of rescue antibiotic (fosfomycin) up to day 3; negative urinary culture result on day 10; reconsultations because of UTI up to day 30; mean composite symptom score on days 3, 7, and 30; time until resolution of symptoms; adverse events; serious adverse events; European quality of life (EQ-5D) health state and visual analogue scale on day 3; working days lost; and overall satisfaction with management of the UTI. Additional time points analysed, which were not prespecified in the protocol but specified before statistical analysis, included days 10 and 30 for resolution and complete absence of symptoms, day 10 for symptom scores, day 3 for use of any antibiotic, and day 30 for use of rescue antibiotics.

The treating doctor and an independent, blinded interviewer carried out telephone interviews on days

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10 and 30, respectively, to assess serious adverse events, adverse events of grade 3 or more severity, any additional unplanned medical visits, including telephone contacts, and co-medications. The clinical diagnosis of pyelonephritis required the occurrence of loin pain and fever, leading to an unplanned outpatient visit. Mid-stream urinary samples obtained on days 0 and 10 were processed according to standard laboratory procedures, using a cut-off of $\geq 10^3$ colony forming units per millilitre for a urinary culture to be considered positive[16]; mixed flora with no predominant microorganism, *Lactobacilli* or *Streptococcus viridans* group were considered a negative result. The supplementary appendix provides details of the baseline assessments, diaries, and scores used.

Statistical analysis

We originally planned to recruit 400 women, but recruitment was slow and financial constraints led us to decide in June 2014 to stop patient recruitment by December 2014, when an expected 260 women would be included. The decision was made without inspecting the data and after repeating the power analysis based on a normal approximation test of proportions,[17] which was less conservative than the simulation based approach originally used. With the original assumption of 70% of women reaching symptom resolution up to day 3 in both groups and the original, prespecified non-inferiority margin of 15% on a risk difference scale, the projected sample size of 260 women would yield a power of 84% to detect non-inferiority at a one sided type I error of 5%. A systematic review and meta-analysis by Falagas et al[18] suggested symptom resolution in approximately 25% of women with UTI receiving placebo and in approximately 60% of women receiving antibiotics. The selected non-inferiority margin of 15% was less than half of the pooled risk difference between antibiotics and placebo of 35%.

The primary outcome was evaluated using a risk difference with a corresponding two sided 95% confidence interval, a one sided normal approximation test for non-inferiority, and a two sided χ^2 test for superiority. We compared secondary outcomes using conventional two sided P values for superiority and corresponding two sided 95% confidence intervals. We used risk differences with χ^2 tests for binary data, Poisson regression with robust standard errors for counts, and linear regression with robust standard errors for continuous data. Kaplan-Meier curves accompanied by hazard ratios from Cox models were used to analyse time to definite symptom resolution and time to antibiotic use. Women were considered to have reached definite symptom resolution in the time-to-event analysis if they reached ≤2 points (slight, very slight, or no problems) on all five components of the symptom severity score and did not report a subsequent flare-up. All women were included in the analysis in the groups to which they were originally allocated (intention to treat analysis), with missing values accounted for by multiple imputation (see supplementary appendix and supplementary table 1).

We performed prespecified subgroup analyses of the primary outcome accompanied by Mantel-Haenszel tests for interaction by age (<45 *v* ≥45 years), symptom severity at baseline (≤20 *v* >20), symptom duration (≤3 *v* >3 days), and presence of a positive urinary culture result at baseline; post hoc subgroup analyses were performed for urine leucocytes (≤++ *v* >++) and the presence of norfloxacin resistant Enterbacteriaceae. In per protocol analyses, we excluded women with protocol deviations, defined as women with no documented intake of at least one dose of study drug, crossovers, and women who used rescue antibiotics before day 3. These analyses were prespecified in a statistical analysis plan before the end of recruitment and inspection of the data.

In sensitivity analyses specified post hoc, we fitted mixed effects models with a random intercept for trial site and multivariable Poisson and linear regression models adjusted for baseline characteristics to estimate treatment effects. For the Poisson regression models we used robust sandwich estimators of standard errors.[19] We then transformed the resulting relative risks to risk differences by combining them with the control group risk in patients allocated to norfloxacin to ensure direct comparability with primary analyses. In further post hoc analyses of women allocated to diclofenac, we compared baseline characteristics and outcomes between those who used antibiotics until day 30 and those who never used antibiotics, determined the time between symptom onset and diagnosis in those with a clinical diagnosis of pyelonephritis, and explored whether blood or urine findings at baseline were associated with pyelonephritis with clinically relevant positive or negative likelihood ratios above 5 or below 0.2, respectively, which could be used to rule in or rule out a future clinical diagnosis of pyelonephritis. All analyses were done in RStudio version 1.0.143 (RStudio: Integrated Development for R. RStudio, Boston, MA www.rstudio.com/).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. We plan to disseminate the results of the research to all the scientific community, including trial participants.

Results

Between 7 February 2012 and 3 December 2014, 253 women were included in the trial. Thirty six patients were recruited in seven single practices, 108 in nine group practices, and 109 in one big medical centre with 17 doctors in the centre of Bern, Switzerland. One hundred and thirty three patients were randomly allocated to diclofenac and 120 to norfloxacin. A total of 125 women (94%) in the diclofenac group and 118 women (98%) in the norfloxacin group. received treatment as allocated. Follow-up until day 30 was complete for 119 (89%) and 112 women

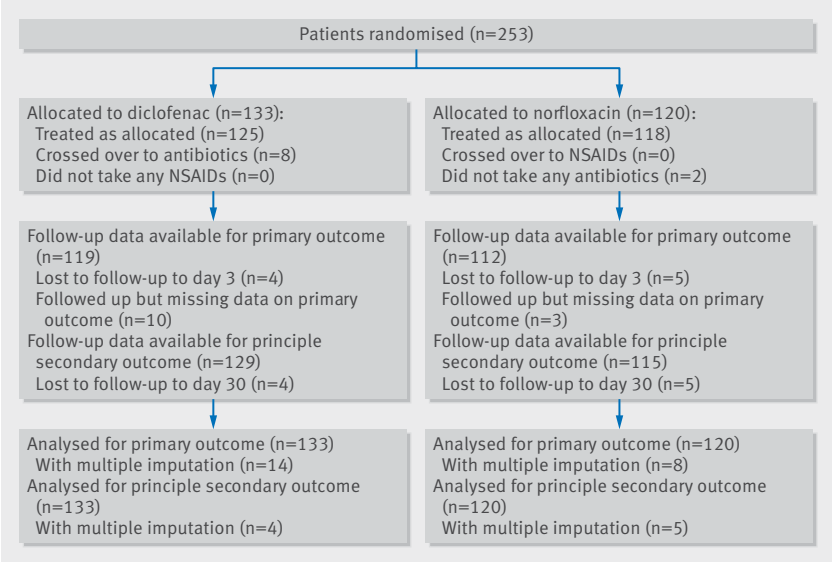

Fig 1 | Participant flow through study. NSAID=non-steroidal anti-inflammatory drug

(93%), respectively (fig 1). Groups were similar (table 1), with a mean age of 36.8 years (SD 14.1), a mean duration of symptoms of 3.4 days (SD 2.7), and a mean composite symptom score of 13.7 points out of 30 (SD 4.0), and urgency, frequency, and dysuria as the most prevalent symptoms. Thirty five urine samples were positive for nitrite (14%) and 191 had more than ++ leucocytes (75%). Urinary cultures gave positive results for 185 urine samples (73%), resulting in a total of 193 isolates, of which 187 (97%) had documented norfloxacin susceptibility. In total, 173 isolates contained Enterobacteriaceae, 160 of which were tested for fosfomycin susceptibility and 158 were found to be susceptible (99%).

Table 2 presents the clinical outcomes. The primary outcome, resolution of symptoms at day 3, was observed in 72 (54%) women in the diclofenac group and 96 (80%) in the norfloxacin group (risk difference 27%, 95% confidence interval 15% to 38%, one sided P=0.98 for non-inferiority, two sided P<0.001 for superiority in favour of norfloxacin group). The principal secondary outcome, use of any antibiotic

Table 1 | Baseline characteristics of participants. Values are means (standard deviations) unless stated otherwise

Characteristics	Diclofenac group (n=133)	Norfloxacin group (n=120)
Age (years)	37.8 (14.2)	35.6 (14.0)
No (%) aged <45 years	94 (71)	89 (74)
Symptom duration: days since UTI onset	3.6 (3.1)	3.2 (2.0)
No (%) with symptom duration ≤3 days	80 (60)	83 (69)
No of UTIs in past 12 months	0.6 (1.1)	0.6 (0.9)
Baseline UTI symptoms (score 0-6):		
Dysuria	3.3 (1.3)	3.3 (1.2)
Urgency	3.7 (1.0)	3.6 (0.9)
Night frequency	2.6 (1.5)	2.6 (1.4)
Day frequency	3.5 (0.9)	3.5 (0.9)
Lower abdominal pain while urinating	2.6 (1.5)	2.6 (1.6)
Back or loin pain	1.1 (1.4)	1.2 (1.5)
Total symptom score	13.7 (3.9)	13.8 (3.8)
No (%) with symptom score ≤20	127 (95)	115 (96)
Blood tests:		
C reactive protein (mg/L)	6.7 (10.5)	8.5 (13.7)
No (%) with C reactive protein >10 mg/L	24 (18)	29 (24)
Leucocytes (10^9/L)	8.5 (2.4)	8.7 (2.2)
Urinary dipstick:		
No (%) positive for nitrites	17 (13)	18 (15)
Median (interquartile range) erythrocytes (+ to ++++)	+++ (++ to ++++)	+++ (++ to ++++)
Median (interquartile range) leucocytes (+ to ++++)	+++ (+++ to ++++)	+++ (+++ to ++++)
No (%) with leucocyte result >++	101 (76)	90 (75)
Urinary culture (No (%))*:		
Negative	36 (27)	31 (26)
Positive†	96 (72)	89 (74)
Escherichia coli	82 (62)	75 (63)
Other Enterobacteriaceae	10 (8)	6 (5)
Staphylococcus saprophyticus	4 (3)	7 (6)
Enterococcus faecalis	1 (1)	6 (5)
βhaemolytic streptococcus group B	1 (1)	1 (1)
Susceptibility to norfloxacin	92 (69)	87 (73)
Enterobacteriaceae	88 (66)	79 (66)
Susceptibility to fosfomycin‡	84 (63)	71 (59)

UTI=urinary tract infection.
*Results missing in one patient in diclofenac group.
†Do not sum up owing to two double mixed infections in the diclofenac group and four double and one triple mixed infection in the norfloxacin group.
‡Relates to Enterobacteriaceae only. Two isolates from the diclofenac group (n=1 *Proteus mirabilis*, n=1 *Enterobacter cloacae*) were not susceptible to fosfomycin.

Table 2 | Primary and secondary outcomes. Values are numbers (percentages) unless stated otherwise

Outcomes	Diclofenac group (n=133)	Norfloxacin group (n=120)	Risk or mean difference (95% CI)	P value
Resolution of symptoms:				
Day 3 (primary outcome)	72 (54)	96 (80)	27 (15 to 38)	<0.001
Day 7	111 (83)	115 (96)	12 (4 to 19)	0.003
Day 10*	126 (95)	116 (97)	2 (−3 to 7)	0.45
Day 30*	127 (95)	111 (93)	−3 (−9 to 3)	0.32
Complete absence of symptoms:				
Day 3	10 (8)	20 (17)	9 (0 to 17)	0.038
Day 7	44 (33)	65 (54)	21 (9 to 34)	0.001
Day 10*	70 (53)	77 (64)	12 (−1 to 24)	0.07
Day 30*	101 (76)	99 (83)	6 (−4 to 17)	0.22
Mean (SD) change of symptom score:				
Day 3	−7.3 (4.7)	−10.3 (4.1)	3.0 (1.9 to 4.1)	<0.001
Day 7	−11.0 (4.8)	−12.6 (4.2)	1.6 (0.5 to 2.7)	0.005
Day 10*	−12.2 (4.3)	−12.9 (4.1)	0.7 (−0.4 to 1.7)	0.20
Day 30	−13.0 (4.4)	−13.1 (4.3)	0.1 (−1.0 to 1.1)	0.88
Use of any antibiotic:				
≤day 3*	58 (44)	116 (97)	−54 (−63 to −44)	<0.001
<day 30 (principal secondary outcome)	82 (62)	118 (98)	−37 (−46 to −28)	<0.001
Use of rescue antibiotic:				
≤day 3	55 (41)	9 (8)	34 (24 to 43)	<0.001
<day 30*	73 (55)	18 (15)	40 (29 to 51)	<0.001
Negative urinary culture at day 10	96 (72)	112 (93)	21 (11 to 30)	<0.001
Reconsultations because of UTI (<day 30)	27 (20)	10 (8)	12 (3 to 20)	0.010
Mean (SD) quality of life (range 0-10):				
EuroQol health state (day 3)	8.8 (2.2)	9.4 (1.5)	0.6 (0.2 to 1.0)	0.005
EuroQol visual analogue scale (day 3)	7.4 (1.9)	8.3 (1.5)	1.0 (0.5 to 1.4)	<0.001
Patient satisfaction with UTI management	5.7 (3.0)	8.2 (2.1)	2.5 (1.9 to 3.2)	<0.001
No of working days lost due to UTI	0.6 (0.8)	0.5 (0.8)	0.2 (−0.1 to 0.5)†	0.18

UTI=urinary tract infection; EuroQol=European quality of life instrument.
Positive differences favour norfloxacin, negative differences favour diclofenac.
*Analysis of additional time points, not prespecified in protocol.
†Relative rate increase calculated from Poisson regression.

up to day 30, was observed in 82 (62%) women in the diclofenac group and 118 (98%) in the norfloxacin group (risk difference 37%, 28% to 46%, P<0.001 for superiority in favour of diclofenac group). Among the 82 women in the diclofenac group who used antibiotics, 58 (71%) decided to take antibiotics during the first three days; 55 of these 58 (95%) women took the rescue antibiotic fosfomycin. Supplementary table 13 presents antibiotics taken in addition to the study drugs for any indication and for recurrent UTI. Five (4%) women in the diclofenac group and 13 (11%) in the norfloxacin group took additional analgesics up to day 3.

Figure 2 presents time to event curves for definite resolution of symptoms (top panel) and use of antibiotics (bottom panel) until day 10 (fig 2 and supplementary table 2). Supplementary figure 1 shows the course of symptom scores. The median time until resolution of symptoms was four days in the diclofenac group compared with two days in the norfloxacin group (hazard ratio 1.64, 95% confidence interval 1.26 to 2.14, P<0.001). The median time until antibiotic use was five and zero days, respectively (10.06, 6.67 to 15.17, P<0.001). Figure 3 shows subgroup analyses for the primary and main secondary outcome. Results appeared consistent across all subgroups. Sensitivity analyses revealed consistent results for the primary and main secondary outcome (see supplementary tables 3-6).

The remaining prespecified outcomes favoured norfloxacin except for change in symptom score on day 30 (P=0.88) and working days lost (P=0.18, table 2). Post hoc analyses of additional time points revealed little evidence of a difference between groups for resolution or complete absence of symptoms on days 10 and 30 or change of symptom score on day 10 (P≥0.07) and strong evidence for a difference in favour of the diclofenac group for antibiotic use up to day 3 (P<0.001, table 2).

Supplementary table 7 shows a post hoc comparison of baseline characteristics of women who had never used antibiotics (n=51) with women who had used any antibiotics until day 30 (n=82) among those randomly allocated to diclofenac. We found little evidence for a difference between groups, except for one component of the symptom composite score. Supplementary table 8 presents a comparison of outcomes. Resolution and complete absence of symptoms at day 3 were more common among women who never used antibiotics (P<0.01), changes of symptom scores were more pronounced at day 3 (P<0.01), reconsultations were less frequent (P<0.01), and scores on quality of life and satisfaction with care were higher (P<0.02). The median time to symptom resolution was three days in women who never used antibiotics and five days in women who used antibiotics (hazard ratio 0.61, 95% confidence interval 0.42 to 0.88, P<0.01, see

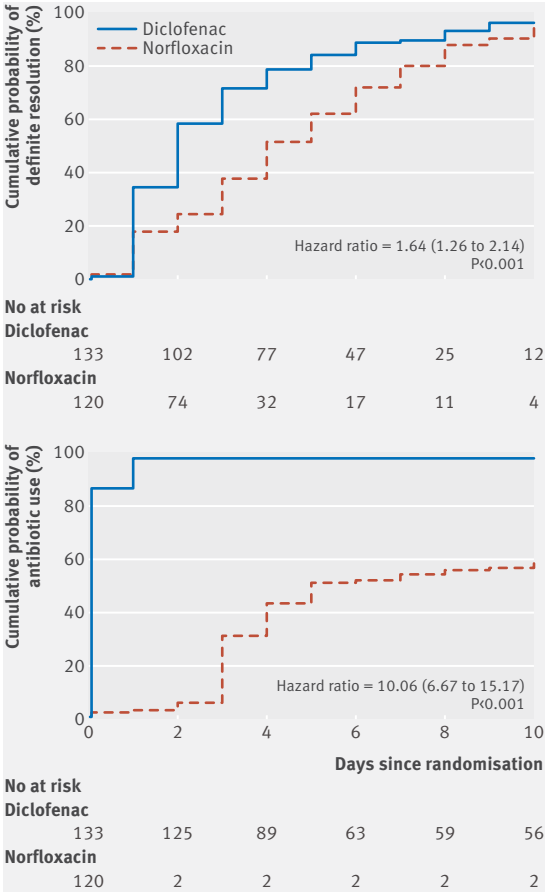

Fig 2 | Kaplan-Meier plot for (top panel) time until definite resolution of symptoms and (bottom panel) time until antibiotic use up to day 10. Nineteen women in the diclofenac group and nine in the norfloxacin group who reached the primary outcome definition of symptom resolution on day 3 subsequently reported a slight flare-up; they were considered to have experienced symptom resolution on day 3 (table 2), but reached definite symptoms later than day 3 (fig 2); six women in the diclofenac group and six in the norfloxacin group who reached the primary outcome definition of symptom resolution on day 3 did not provide enough information to derive the time point of definite resolution and were censored at day 0 (five in each group) or day 10 (one in each group)

supplementary figure 2 and supplementary table 9). Thirty four urinary cultures had been positive at baseline among women who never used antibiotics, and the results for 16 of these spontaneously became negative on day 10 (47%).

Table 3 presents adverse events that resulted in reconsultations: 43 events in 41 women in the diclofenac group (31%) and 22 events in 21 women in the norfloxacin group (18%). Adverse events related to UTI were more common in the diclofenac group (P=0.01), with six cases of clinically diagnosed pyelonephritis in the diclofenac group (5%) and none in the norfloxacin group (P=0.03); one woman with clinically diagnosed pyelonephritis in the diclofenac group was classified to have experienced a serious adverse event as she was admitted to hospital to receive intravenous antibiotic treatment. Supplementary table 10 shows a comparison of baseline characteristics of women with and without pyelonephritis in the diclofenac group. Supplementary table 11 presents the timing of administered antibiotics since symptom onset and randomisation, and the type of antibiotic used in the six women with pyelonephritis. The median time from symptom onset to clinical diagnosis of pyelonephritis was 5.5 days (range 5.0-8.0 days). A post-hoc analysis revealed that C reactive protein levels >10 mg/L at baseline were observed in 21 women in the diclofenac group without pyelonephritis (17%) and in three women with pyelonephritis (50%, see supplementary table 10). This resulted in a positive likelihood ratio of 3.02 (95% confidence interval 1.07 to 5.98) for C reactive protein levels >10 mg/L. None of the remaining analysed characteristics was associated with statistically significant and clinically relevant positive or negative likelihood ratios suitable to rule in or rule out a future diagnosis of a pyelonephritis (see supplementary table 12). Supplementary table 14 shows that mean symptom scores for women who developed pyelonephritis were higher at baseline and day 3 compared with women who did not develop pyelonephritis, but differences subsequently diminished. Supplementary figure 3 graphically shows the course of symptom scores in patients with and without pyelonephritis in the diclofenac group.

Discussion

In this randomised, double blind trial in women with uncomplicated lower urinary tract infection (UTI), symptomatic treatment with the non-steroidal anti-inflammatory drug (NSAID) diclofenac was inferior to antibiotic treatment with norfloxacin in controlling symptoms. Those treated with diclofenac were 27% less likely to have symptom resolution at day 3 after randomisation and 12% less likely to have symptom resolution at day 7 after randomisation, with higher mean symptom scores, more frequent reconsultations, a higher incidence of clinically diagnosed pyelonephritis, and lower patient satisfaction than those in the norfloxacin group. Conversely, women who received diclofenac were 37% less likely to receive antibiotics until day 30 after randomisation.

A meta-analysis of five trials concluded that antibiotics are clinically superior to placebo in women with uncomplicated lower UTI.[18] Our trial, in conjunction with the recently published trial by Gágyor et al,[10] suggests that antibiotics are also clinically superior to symptomatic treatment with NSAIDs. This contrasts with the findings of a small pilot trial by Bleidorn et al,[9] where clinical outcomes of treatment with ibuprofen were similar to those of antibiotic treatment with ciprofloxacin. The pilot trial triggered both our trial and that by Gágyor et al.[10] Both pivotal trials were adequately powered but failed to detect non-inferiority of NSAIDs compared with antibiotics for symptom control. Importantly, both trials suggest that symptomatic treatment with NSAIDs is associated

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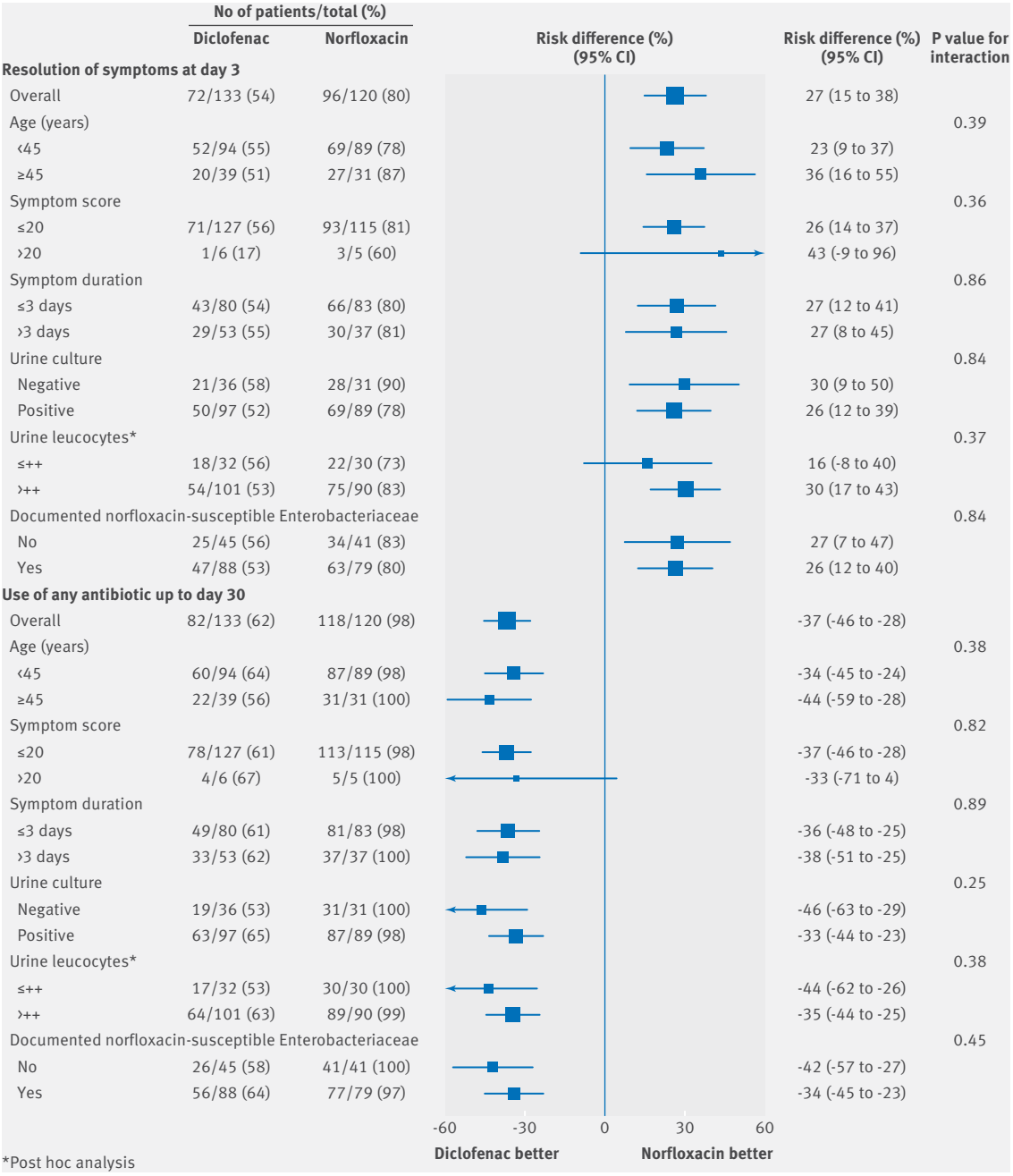

Fig 3 | Subgroup analyses of primary outcome (resolution of symptoms at day 3) and main secondary outcome. Positive differences favour norfloxacin, negative differences favour diclofenac

with an increase in the risk of clinically diagnosed pyelonephritis, which translates into a number needed to harm of 23 compared with antibiotic treatment in our trial. The risk of clinically diagnosed pyelonephritis in patients allocated to NSAIDs appeared higher than the risk observed in patients allocated to placebo in antibiotic trials by Christiaens et al and Ferry et al.[20 21] Although indirect comparisons like these should be interpreted with caution,[22] they would be in line with recent evidence suggesting that NSAIDs may actually be harmful in patients with infectious diseases,[23-25] despite potential antibacterial activities of diclofenac[26] and ibuprofen.[27] On the beneficial side, both pivotal trials suggest that antibiotic use can be halved on average by initial symptomatic treatment with NSAIDs, with a corresponding number needed to treat of 2 to prevent one instance of antibiotic use. We provided women with a rescue antibiotic for discretionary use after completion of the study drug and reaching the primary endpoint. This may have facilitated antibiotic use in the NSAID treatment arm of our trial. None the less, given the high global incidence of UTIs, the observed reduction in antibiotic use is highly relevant and is likely to immediately decrease resistance rates for *Escherichia coli* and even other microorganisms in the affected population.[28]

Table 3 | Adverse events resulting in reconsultations up to 30 days

Adverse events	No (%) in diclofenac group (n=133)	No (%) in norfloxacin group (n=120)	Risk difference (95% CI)	P value*
Related to UTI	26 (20)	10 (8)	11 (3 to 20)	0.012
Persistent symptoms	16 (12)	4 (3)	9 (2 to 15)	0.011
Additional symptoms	6 (5)	2 (2)	3 (−1 to 7)	0.29
Recurrent UTI†	5 (4)	4 (3)	0 (−4 to 5)	1.00
Pyelonephritis‡	6 (5)	0 (0)	5 (1 to 8)	0.031
Other adverse event	17 (13)	12 (10)	3 (−5 to 11)	0.56
Exanthema	1 (1)	2 (2)	−1 (−4 to 2)	0.61
Vaginitis	3 (2)	0 (0)	2 (0 to 5)	0.25
Gastrointestinal symptoms§	3 (2)	3 (3)	−0 (−4 to 4)	1.00
Low back pain¶	5 (4)	2 (2)	2 (−2 to 6)	0.45
Viral infection	1 (1)	3 (3)	−2 (−5 to 1)	0.35
Trauma	3 (2)	1 (1)	1 (−2 to 4)	0.62
Miscellaneous**	3 (2)	1 (1)	1 (−2 to 4)	0.62

UTI=urinary tract infection.
Numbers do not add up as patients experienced at least one adverse event for each category.
*Two sided Fisher's exact test.
†Recurrent UTI was defined as additional visits after day 14 because of recurrent UTI symptoms after symptoms had resolved by day 10, and the physician decided to treat with antibiotics.
‡One patient in the diclofenac group was admitted to hospital on day 4 because of pyelonephritis.
§Includes one case of diverticulitis in the norfloxacin group.
¶Considered to be of musculoskeletal origin by treating doctor.
**Includes one case of external otitis and two cases of tonsillitis in the diclofenac group and one case of hair loss in the norfloxacin group.

The increasing antibiotic resistance among uropathogens in general and *E coli* (the most common uropathogen) in particular is a global concern. Many studies show a clear correlation between antibiotic consumption and rising resistance rates. Accordingly, antibiotics are often withheld in cases of self limited, benign bacterial diseases such as acute otitis media, sinusitis, and traveller's diarrhoea at the cost of a prolongation of symptoms by typically 1-3 days.[29-36] Our results in women with uncomplicated lower UTI are well in line with the prolongation of symptoms observed with symptomatic treatment of these conditions. As many women in the diclofenac group resorted to antibiotic treatment in our trial, a strategy of selectively deferring rather than completely withholding antibiotic treatment may be preferable for uncomplicated lower UTI.[37] This can be achieved through a shared decision making process, during which clinicians inquire about their patients' ideas and expectations about antibiotic treatment for uncomplicated UTI and also explore the option of delaying antibiotic use as a treatment strategy.

Subgroup analyses did not provide evidence for any clinically relevant treatment by subgroup interactions. In particular, in contrast with the study by Gágyor et al,[10] reduction in antibiotic prescription was comparable in women with and without positive urinary culture results. Testing initial urine samples for other biomarkers associated with UTI, such as heparin binding protein, interleukin 6, acetic acid, trimethylamine, xanthine oxidase, myeloperoxidase, or others,[38-40] might have resulted in promising treatment by subgroup interactions, but these tests are not yet established in clinical practice, and we are unaware of any evidence to suggest that such interactions would be likely. In subgroup analyses, there were no relevant differences in baseline characteristics that would allow an early identification of women likely to benefit from diclofenac alone. However, in additional post hoc analyses, which were purely hypothesis generating, we found that the clinical diagnosis of pyelonephritis was established not earlier than five days after symptom onset, and that C reactive protein values >10 mg/L were more common at baseline in women who subsequently had a diagnosis of pyelonephritis. Taken together, these exploratory findings could support a tailored strategy of immediate antibiotic use in women with C reactive protein levels >10 mg/L and symptomatic treatment in remaining women for up to three or four days after symptom onset, followed by deferred, selective antibiotic use in those women who did not show a clear improvement by then. Naturally, such a tailored strategy would need to be evaluated in an appropriately powered randomised trial.

Strengths and limitations of this study

Our trial should be interpreted in view of its strengths and limitations. Strengths are its randomised double blind design with appropriate concealment of allocation; blinding of patients, therapists, and outcome assessors; the low loss to follow-up; the robustness of results in a series of sensitivity analyses; and the multicentre primary care setting. The premature termination of patient recruitment before reaching the initially planned sample size is an obvious limitation. However, the decision to stop recruitment was made without inspecting the data and is therefore unlikely to have biased our findings.[41] Despite the smaller than originally planned sample size, our results are completely unequivocal. The self report questionnaire used to ascertain severity of symptoms was developed based on questionnaires described by Clayson et al[12] and Little et al,[13] which were available at the time of designing our trial. Women had to rate the severity of dysuria, frequency, urgency, and abdominal pain when passing urine and pain or tenderness in the lower back or loin on Likert scales from 0 to 6. The resulting summary score from 0 to 30 used to assess symptom severity as one of the secondary outcomes was not psychometrically validated and should

therefore be considered exploratory. The primary outcome of symptom resolution at day 3 was defined as slight, very slight, or no problems reported for all five components.[12 14 15] As these components assessed well established concepts and the calculation of a summary score was not necessary, we consider our primary outcome to be valid. A final limitation is that our results are not generalisable to countries and clinical settings with lower rates of susceptibility, which could decrease the effectiveness of antibiotics and render symptomatic treatment with NSAIDs less inferior.

Conclusions

Symptomatic treatment is inferior to antibiotic treatment for women with uncomplicated lower UTI in an ambulatory setting, as it increases median symptom duration by two days and is likely to be associated with an increased risk of clinically diagnosed pyelonephritis. The observed clinically relevant reduction in antibiotic use, which would likely contribute directly to decreasing resistance rates in the affected population, suggests that alternative approaches of combining symptomatic treatment with deferred, selective antibiotic use should be developed and tested in future trials.

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Ethical approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee and the Swiss Agency for Therapeutic Products, swissmedic.

Data sharing: The statistical analysis plan and the final version of the study protocol are available from the corresponding author. Anonymised patient level data will be made available from the corresponding author at the Institute for Infectious Diseases, University Bern on reasonable request. Consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low. No additional data are available.

Transparency: The lead authors (AK and PJ) affirm 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.

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Supplementary information: Investigator and committee members, collaborators, additional methods, tables, and figures