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Phytotherapy (BNO 1045) of Acute Lower Uncomplicated Urinary Tract Infection in Women Normalizes Local Host Responses

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Keywords
BNO 1045 · Phytotherapy · Uncomplicated urinary tract infection · Urine cytokines

Abstract

Introduction: Acute lower uncomplicated urinary tract infection (uUTI) affects a large proportion of women. Increased antimicrobial resistance has created an urgent need for novel therapeutics and the phytotherapeutic drug BNO 1045 (Canephron® N) has previously been shown to be noninferior to standard antimicrobial stewardship. This sub-analysis from a randomized, double-blind, controlled phase III noninferiority clinical trial using BNO 1045 versus fosfomycin to treat uUTI aimed to determine how urine cytokine levels are altered by the two different treatments. ***Methods:*** Urine samples from a predefined subset of women diagnosed with uUTI (18–70 years) and treated with BNO 1045 (n = 58) or fosfomycin (n = 69) were analyzed for urine levels of IL-6 and IL-8, using analyte-to-creatinine ratios. ***Results:*** BNO 1045 treatment showed similar effects to fosfomycin treatment in reducing both urine IL-6 and IL-8 levels. Mean IL-6 and IL-8 levels were markedly reduced in all patients regardless of treatment. BNO 1045 treatment decreased urine IL-8 significantly (p = 0.0142) and showed a trend toward reduction of urine IL-6 (p = 0.0551). Fosfomycin treatment reduced both IL-6 and IL-8 levels significantly (p = 0.0038, <0.0001 respectively). ***Conclusion:*** BNO 1045 is, in addition to reducing symptoms, comparable to fosfomycin treatment in reducing the local inflammatory response associated with uUTI.

Introduction

According to current guidelines, antimicrobials are the gold standard treatment for urinary tract infections, and their efficacy has been shown in several clinical trials [1, 2]. However, since antimicrobials have several adverse effects on the normal flora and contribute to the growing problem with antimicrobial resistance, it is important to use antimicrobials sparsely and use nonantibiotic alternatives whenever possible. Acute lower uncomplicated urinary tract infections (uUTIs) are often self-limiting infections and thus prescription of antimicrobials may often not be necessary [3]. In addition, several clinical trials indicate high efficacy of alternative therapies, e.g., anti-inflammatory drugs [1, 2, 4, 5]. Consequently, it has been proposed that symptom relief by ameliorating the inflammatory host response should be the primary

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outcome of uUTI management as the bacteria are often cleared without antimicrobial intervention [6]. If bacteriuria should persist post-treatment, it may lead to asymptomatic bacteriuria, which is considered harmless and may serve as a protective carrier state against recurrent infections [7, 8].

During uUTI, several cytokines and chemokines that influence the inflammatory state of the urinary bladder are triggered, including interleukin (IL)-8 and IL-6. IL-8 is a neutrophil chemoattractant that leads to the recruitment and infiltration of neutrophils to the site of infection (pyuria) which is paralleled by increased urine IL-8 levels [9, 10]. IL-6 is an acute phase reactant and a pyrogen that is considered to reflect more severe infection with tissue engagement [11–14]. Previous studies have discussed that triggered urine IL-6 levels may be used as a predictive biomarker for a more severe course of cystitis or the development of pyelonephritis [13].

Recently, a large randomized clinical trial (RCT) showed a significant reduction of uUTI symptoms by BNO 1045 with effects comparable to the antimicrobial substance fosfomycin [15]. BNO 1045 (Canephron® N) is a phytotherapeutic drug containing centaury herb (*Centaurium erythraea* Rafn, *herba*), lovage root (*Levisticum officinale* Koch, *radix*), and rosemary leaf (*Rosmarinus officinalis* Linné, *folium*) that has been approved as a remedy to treat uUTI in over 31 countries. BNO 1045 is known to have "multi-target" effects including spasmolytic, diuretic, anti-oxidative, anti-adhesive, anti-inflammatory, and anti-nociceptive effects [16–20]. As preclinical data indicate an inhibitory influence of BNO 1045 on pro-inflammatory mediators [19], we investigated how BNO 1045 affects urine IL-6 and IL-8 levels and compared it to patients treated with convential fosfomycin treatment.

Materials and Methods

Patients and Study Design

In a RCT with 659 female patients, BNO 1045 was shown to be noninferior to fosfomycin regarding efficacy in the treatment of uUTI using a noninferiority margin of 15% [15]. The present explorative study investigated the local host response from a predefined subset of patients (n = 154). The study sites included in this explorative study needed to fulfill appropriate urine storage facilities (−80°C freezer) and had to be located in Germany or Poland, as shipment of samples from Ukraine was not possible due to customs' requirements. In total, patients and samples from 88 patients from Germany and 66 patients from Poland took part in this explorative sub-study. Patient urine samples were collected on day 1 (visit 1, baseline which means start of treatment) and on day 8 (visit 3, end of treatment). Symptom scoring was recorded according to the Acute Cystitis Symptom Score (ACSS) questionnaire [21, 22]. At both visits, urine samples were analyzed for urine IL-6, IL-8, as well as bacterial growth. Patients with missing data of any parameter (e.g., urine culture, urinary cytokines, symptom scoring) were excluded from the analysis (n = 24). Two further patients were excluded due to baseline data not compatible with uUTI, and 1 patient had host response data suspicious of unspecified concomitant systemic inflammation. A total of 127 patients were evaluable, 58 patients in the BNO 1045, and 69 patients in the fosfomycin study arms. Patient characteristics and findings at baseline are described in Table 1.

Urine Sampling

Four urine samples (approximately 4 mL) were obtained at visit 1 and visit 3 for analysis of inflammatory parameters and were shipped frozen (−80°C) to the central laboratory MLM Medical Labs (Mönchengladbach). IL-6 and IL-8 were quantified by multi-array approach (i.e., Meso Scale Discovery technology) and normalized to urine creatinine levels to avoid biased values due to differences in urine dilutions. Bacterial counts were evaluated categorically (colony-forming units per mL of urine of $<10^3$, 10^3, 10^4, 10^5, 10^6, or $>10^6$).

Statistics

SAS™ 9.4 (SAS Institute 2010) was used for statistical analysis and graphical presentations of results. Wilcoxon matched-pairs signed-rank test was used for paired comparisons and the Mann-Whitney U test for group-wise comparisons. Fisher's exact test was used for comparison of frequencies. A p value ≤0.05 was considered significant. All analyses are based on all patients with evaluable data in the respective variable. In order to analyze the linear relation between symptom severity and cytokine concentration in urine, Pearson's correlation coefficients were calculated.

Results

To analyze the comparability of the treatment groups, we first investigated whether baseline characteristics were equal between the two study arms (Table 1). No obvious differences were observed between the two treatment arms of our subset of patients. In addition, there were no differences for either urine IL-6 or IL-8, and there were no detectable differences in symptom scores nor bacterial burden at baseline.

In line with previous studies of host responses in uUTI, patients had elevated urine IL-6 and IL-8 levels at enrollment. In a combined analysis of the two study arms, treatment resulted in a highly significant reduction of urine cytokine concentrations (Fig. 1, 2). When analyzed separately, both treatments caused a reduction of urine IL-8 and IL-6 levels (BNO 1045 study arm, p = 0.0142 and 0.0551, respectively; fosfomycin study arm, $p < 0.0001$ and 0.0038, respectively). These results indicate that both BNO 1045 and fosfomycin treatment reduce the inflammatory response during uUTI.

Table 1. Patient characteristics

Characteristic	Category	BNO 1045 (*N* = 58)	FT (*N* = 69)	Total (*N* = 127)
Age, years	Mean (SD)	40.6 (14.40)	42.8 (14.70)	41.8 (14.55)
	Median (range)	40.5 (18–70)	47.0 (18–68)	43.0 (18–70)
Race, *n* (%)	Caucasian	55 (94.8)	68 (98.6)	123 (96.9)
	Other[a]	3 (5.2)	1 (1.4)	4 (3.1)
Weight, kg	Mean (SD)	72.3 (19.37)	69.9 (15.58)	71.0 (17.39)
	Median (range)	68.4 (46–147)	67.0 (47–126)	68.0 (46–147)
Height, cm	Mean (SD)	165.8 (6.59)	164.9 (5.91)	165.3 (6.22)
	Median (range)	165.5 (150–184)	164.8 (149–184)	165.0 (149–184)
Smoking status, *n* (%)	Smoker	17 (29.3)	12 (17.4)	29 (22.8)
	Nonsmoker	36 (62.1)	47 (68.1)	84 (65.4)
	Ex-smoker	5 (8.6)	10 (14.5)	15 (11.8)
Urine culture test, CFU/mL (%)	$<10^3$	9 (15.5)	10 (14.5)	19 (15.0)
	10^3	19 (32.8)	21 (30.4)	40 (31.5)
	10^4	11 (19.0)	14 (20.3)	25 (19.7)
	10^5	8 (13.8)	11 (15.9)	19 (15.0)
	10^6	8 (13.8)	11 (15.9)	19 (15.0)
	$>10^6$	3 (5.2)	2 (2.9)	5 (3.9)
Menopausal status, *n* (%)	Pre-menopausal	48 (82.81)	50 (72.5)	98 (77.2)
	Post-menopausal	10 (17.2)	19 (27.5)	29 (22.8)
Sexual activity, *n* (%)	Not active	17 (29.3)	20 (29.0)	37 (29.1)
	Active	41 (70.7)	49 (71.0)	90 (70.9)
Childbearing potential	Yes	42 (72.4)	44 (63.8)	86 (67.7)
	No	16 (27.6)	25 (36.2)	41 (32.3)
IL-6, ng/g urine creatinine	Mean (SD)	5.48 (14.70)	4.66 (11.44)	5.04 (12.99)
	Median (range)	0.75 (0.13–81.17)	0.78 (0.09–68.46)	0.77 (0.09–81.17)
IL-8, ng/g urine creatinine	Mean (SD)	625.8 (1,061.5)	691.8 (1,095.58)	661.6 (1,076.4)
	Median (range)	133.8 (10.1–4,724.0)	267.2 (12.5–6,206.5)	204.0 (10.1–6,206.5)
ACSS – sum score of typical domain	Mean (SD)	11.0 (2.06)	11.0 (2.15)	11.0 (2.10)
	Median (range)	11 (7–16)	11 (6–16)	11 (6–16)

FT, fosfomycin trometamol; FAS, full analysis set; *N*, number of patients in treatment group; *n*, number of patients with data; %, percentage based on *N*. [a]Grouped into one category for data protection reasons.

Since eligible patients for the study had a sum score of ≥6 for the three main symptoms (dysuria, pollakisuria, urgency) reported on the ACSS typical domain, we analyzed whether the severity of symptoms, as determined by the sum score of the six typical symptoms at baseline and end of treatment, correlated with the amount of urine cytokine concentrations (Fig. 3, 4). Only a weak linear correlation between urine cytokine concentrations and the sum scores of the typical domain of the ACSS could be observed (IL-6 = Pearson's rho: 0.1600 and IL-8 = Pearson's rho: 0.2858); however, both were statistically significant.

Discussion/Conclusion

BNO 1045 treatment has been shown to be noninferior to fosfomycin treatment using a 15% noninferiority margin [15]. 83.5% of patients receiving BNO 1045 did not need additional antibiotic prescription during an extended time period and the adverse events were few and similar in both groups [15]. These data was confirmed by a recently published real-world data study demonstrating that BNO 1045 treatment was not only associated with reduced additional antibiotic prescriptions within 31–365 days after diagnosis but also with significantly fewer recurrences of UTIs [21].

Infection of the urinary bladder triggers a substantial inflammatory host response, including the cytokines IL-6, a well-known acute phase reactant and pyrogen, and IL-8, a neutrophil chemoattractant. Both, urine IL-6 and IL-8 levels increase dramatically within hours of infection during uUTIs [22, 23] and IL-6 is a biomarker that can differentiate UTI severity [14]. Both cytokines promote inflammation, which in turn leads to sensitization of sensory neurons and thereby contributes to

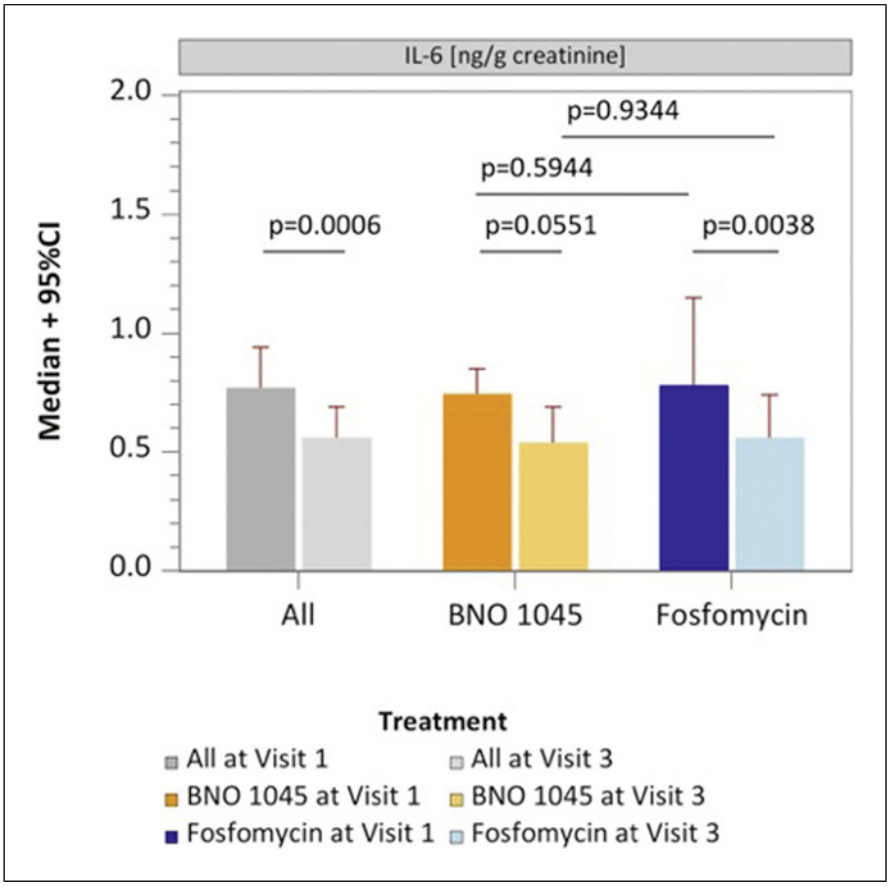

Fig. 1. Urine IL-6 in female patients with uUTI and treated with BNO 1045 (CLR) or fosfomycin (FT) at baseline (visit 1) and at end of treatment (visit 3).

symptoms such as dysuria, pollakisuria, and urgency [24]. In the present study, urinary IL-6 and IL-8 were analyzed on day 1 (visit 1; before treatment) and on day 8 (visit 3; end of treatment) in a subgroup of patients who fulfilled the same inclusion/exclusion criteria (e.g., ACSS sum score ≥6 for the three main uUTI symptoms dysuria, pollakisuria, and urgency) as the entire study population to elucidate the previously reported clinical efficacy of BNO 1045.

Analysis of the baseline values for urine IL-6 and IL-8 as well as for symptom scoring or bacterial burden at baseline revealed no differences. In both groups, treatment with either BNO 1045 or fosfomycin reduced the inflammatory host response, i.e., urine IL-6 and IL-8, which is in line with preclinical data showing inhibitory effects on cytokine release [19]. The reduction of urinary cytokines, as observed in this study, provides at least in part an explanation for the clinical efficacy [15] and effectiveness [21] of BNO 1045. In addition, the fosfomycin study arm could be employed as a control for the effects of standard treatment practice. Infection triggered a local host response as expected in symptomatic patients, which was followed by a reduction to a normalized response after treatment. We thereby demonstrated that BNO 1045 treatment, in addition to symptom relief, was approximately similar to fosfomycin treatment in reducing inflammatory responses. This conclusion is supported by the decrease of IL-8, which showed a statistically significant decrease in both treatment groups. These results also suggest a diminished neutrophil response, which are known to be the main driver of inflammation during bladder infection [25]. For IL-6, the decrease was statistically significant in the fosfomycin treatment arm while the decrease under BNO 1045 treatment did not reach statistical significance, indicating that there are potential different mechanisms of protection of the two drugs.

Besides promoting inflammation, urinary cytokines might also provide an objective and simple measure of uUTI symptom severity. To establish whether IL-6 and IL-8 qualify as such, linear correlation between symptom severity and cytokine concentration was analyzed. Based on this patient subgroup, a correlation of the cytokines IL-6 or IL-8 and the severity of the symptoms, measured as sum score of the typical domain of ACSS, could not be detected. There was however a statistically significant but weak correlation

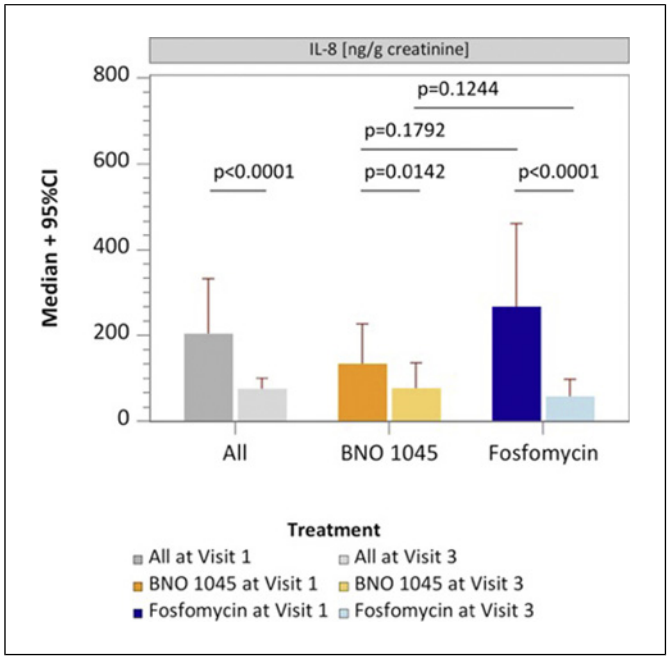

Fig. 2. Urine IL-8 in female patients with uUTI and treated with BNO 1045 (CLR) or fosfomycin (FT) at baseline (visit 1) and at end of treatment (visit 3).

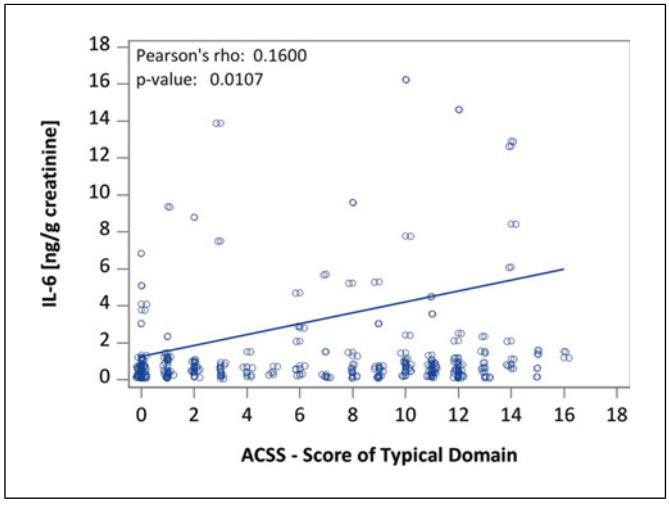

Fig. 3. Correlation between urine concentration of IL-6 (ng/g urine creatinine) and summary score of typical symptoms determined by the Acute Cystitis Symptom Score (ACSS) questionnaire, both treatment groups and both visits (visit 1 and visit 3).

between these parameters. A possible explanation for this could be that the dynamics of the host response and symptoms follow different time courses. To test this hypothesis, more time points in addition to the available ones (day 1 and 8) might be necessary in addressing this hypothesis.

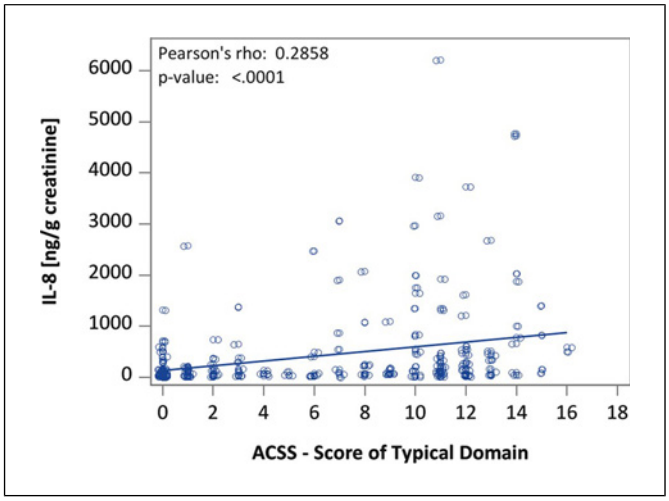

Fig. 4. Correlation between urine concentration of IL-8 (ng/g urine creatinine) and summary score of typical symptoms determined by the Acute Cystitis Symptom Score (ACSS) questionnaire, both treatment groups and both visits (visit 1 and visit 3).

Thus, limitations of the present study do exist, the most prominent one being that a placebo arm of the trial is missing. As previously mentioned, uUTIs are often self-limiting and may resolve independently of the respective treatment, and a placebo-controlled RCT is warranted. It has been estimated that approximately 30% of patients receiving placebo treatment have a rapid clinical improvement [26]; however, no data exist whether there are any effects on epithelial/urothelial host responses. IL-6 and IL-8 are supposed to be biomarkers of uUTI severity, yet in vitro and in vivo studies suggest that other cytokines including IL-1β and IL-17 may be key drivers of UTI pathogenesis and therefore should serve as additional read-outs for further studies investigating the pathophysiology of uUTI and treatment efficacy of BNO 1045 [27, 28].

Conclusion

In conclusion, the data from this study confirm the published efficacy and effectiveness of BNO 1045 in the treatment of uUTI and indicate that anti-inflammatory effects of BNO 1045 observed in vitro are clinically relevant regarding symptom relief in patients suffering from uUTI.

Acknowledgments

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Statement of Ethics

This was a double-blind, controlled, double-dummy, parallel-group, randomized, multicenter, multinational phase III non-inferiority trial, conducted in 51 centers in Europe: 16 in Germany, 22 in Ukraine, and 13 in Poland (EudraCT number 2013-004529-99, ClinicalTrials.gov number NCT02639520). This study protocol was initially reviewed and approved by the Ethics Committee of the medical faculty Gießen (approval number 150/15). Subsequently, the trial was approved by the Commissions of Bioethics in Ukraine by the following institutions: Institute of Nephrology, National Academy of Medical sciences of Ukraine (1/EK-2016), Ivano-Frankivsk City Clinical Hospital and Ivano-Frankivsk Central Clinical Hospital, Ivano, Frankivsk (N21/60/2026 and N44 2016.04.28), Institution of Communal Property of the Region, Mykolaiv (N5, 2105042016), National Military Medical Clinical Center (N1/4/16), Viddilkova Clinical Hospital at Station Zaporizhzhia – 2 of the State Enterprise (N004-1P-016), Regional Clinical Hospital named after I. I. Mechnikov, Dnipropetrovsk (N553/16), Zaporizhzhia Regional Hospital, Zaporizhzhia (N76, 18032026) National Academy of Medical Sciences of Ukraine, Kyiv (N4, 01042016), Polyclinic of Limited Liability Co., Kharkiv (N1-03-30032016), Lviv Clinical Hospital, Lviv (N1577/0), Municipal Clinical Emergency Hospital, Lviv (N42.6.07042016), Kyiv Clinical Hospital on Railway Transport #1 Healthcare Center (N34, 20260427), Kyiv City Clinical Hospital #3, Urology Department, Kyiv (N41-149/KE), City Clinical Hospital, Odessa (8042016), Municipal Institution of Ternopil Regional Council, Ternopil University Hospital, Ternopil (N87, 27042016), Institute of General and Emergency Surgery named after V. T. Zaitsev NAMS of Ukraine, Kharkiv (15032016), Oleksandrivska Clinical Hospital of Kyiv, Kyiv (N95, 1503206), Treatment and Diagnostic Center, Adonis, Plus, Outpatient Department, Kyiv (N14, 17082016). In Germany, the trial was approved by the Ethic Committees of the Medical Faculty, Justus Liebig University Gießsen (15/0368), Medical Association of Baden-Würtemberg (B-AM-205-120), Medical Association of Bavaria (7/15160) Office of the Ethics Committee of the Federal State Berlin (15/0368-EK), Medical Association Hamburg (MC-268/15), Medical Association Hesse (MC200/2025), Friedrich Schiller University Jena (15/8/4526), Medical Association Lower Saxony (N/A), Medical Association North Rhine (2015293), Medical Association Rhineland-Palatinate (837.334.14 [10102]), Medical Faculty, University of Rostock (LK-2025-0045), Saxonian Medical Association (EK-AMG-MCB-90/15-1), and the Medical Association Westphalia-Lippe and of the Medical Faculty, University of Münster (2016-192-b-A). In Poland, the trial was approved by the Bioethics Committee at the Lower Silesian Chamber of Physicians (24052016). All patients provided written informed consent to participate.

Conflict of Interest Statement

This clinical trial was sponsored by Bionorica SE, Germany, and coordinated by the contract research organization Clinipace Worldwide (CPWW). Employees of Bionorica SE had a role in trial design, data analysis, and data interpretation. F.M.W. reports personal consulting fees and other fees from Bionorica SE during the conduct of the study; personal fees outside the submitted work from Achaogen, AstraZeneca, Janssen, LeoPharma, MerLion, MSD, OM Pharma/Vifor Pharma, Pfizer, RosenPharma, and VenatoRx; and other fees outside the submitted work from Enteris BioPharma, Helperby Therapeutics, and Shionogi. K.G.N. reports personal consulting fees from Bionorica SE during the conduct of the study and personal fees outside the submitted work from Adamed, Apogepha, DaiichiSankyo, Enteris, GSK, Helperby, Hermes, Medice, MerLion, OM Pharma/Vifor, Paratek, Roche, Saxonia, and Zambon. D.A.-S., H.S., and M.H. are employees of Bionorica SE. D.S.C.B. has no conflicts to declare.

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Author Contributions

F.W., M.H., H.S., D.A.-S., and K.N. conceptualized the study. D.S.C.B., F.W., M.H., H.S., D.A.-S., and K.N. analyzed the data and wrote the original draft of the manuscript. D.S.C.B. and M.H. revised and edited the final manuscript. H.S. analyzed statistics. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare funding and support have been provided by Bionorica SE to aid in the conduct of the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Kronenberg A, Butikofer L, Odutayo A, Muhlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ. 2017 Nov 7;359:j4784.

2 Vik I, Bollestad M, Grude N, Baerheim A, Damsgaard E, Neumark T, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomized non-inferiority trial. PLoS Med. 2018 May;15(5):e1002569.

3 Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomized placebo controlled study. Scand J Infect Dis. 2004;36(4):296–301.

4 Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ. 2015 Dec 23;351:h6544.

5 Bleidorn J, Hummers-Pradier E, Schmiemann G, Wiese B, Gagyor I. Recurrent urinary tract infections and complications after symptomatic versus antibiotic treatment: follow-up of a randomised controlled trial. Ger Med Sci. 2016;14:Doc01.

6 Bonkat GRP, Bartoletti R, Bruyère F, Geerlings S, Köves B, Wagenlehner F, et al. EAU guidelines on urological infections. European Association of Urology; 2017. p. 22–6.

7 Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis. 2012 Sep;55(6):771–7.

8 Koves B, Cai T, Veeratterapillay R, Pickard R, Seisen T, Lam TB, et al. Benefits and harms of treatment of asymptomatic bacteriuria: a systematic review and meta-analysis by the European association of Urology urological infection guidelines panel. Eur Urol. 2017 Dec;72(6):865–8.

9 Ko YC, Mukaida N, Ishiyama S, Tokue A, Kawai T, Matsushima K, et al. Elevated interleukin-8 levels in the urine of patients with urinary tract infections. Infect Immun. 1993;61(4):1307–14.

10 Harada A, Sekido N, Akahoshi T, Wada T, Mukaida N, Matsushima K. Essential involvement of interleukin-8 (IL-8) in acute inflammation. J Leukoc Biol. 1994 Nov;56(5):559–64.

11 Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990 Feb 1;265(3):621–36.

12 Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295–a95.

13 Sunden F, Wullt B. Predictive value of urinary interleukin-6 for symptomatic urinary tract infections in a nursing home population. Int J Urol. 2016 Feb;23(2):168–74.

14 Sunden F, Butler D, Wullt B. Triggered urine interleukin-6 correlates to severity of symptoms in nonfebrile lower urinary tract infections. J Urol. 2017 Jul;198(1):107–15.

15 Wagenlehner FM, Abramov-Sommariva D, Holler M, Steindl H, Naber KG. Non-antibiotic herbal therapy (BNO 1045) versus antibiotic therapy (fosfomycin trometamol) for the treatment of acute lower uncomplicated urinary tract infections in women: a double-blind, parallel-group, randomized, multicentre, non-inferiority phase III trial. Urol Int. 2018;101(3):327–36.

16 Haloui M, Louedec L, Michel JB, Lyoussi B. Experimental diuretic effects of rosmarinus officinalis and Centaurium erythraea. J Ethnopharmacol. 2000 Aug;71(3):465–72.

17 Brenneis C, Haunschild J. Spasmolytic activity of Canephron® N on the contractility of isolated urinary bladder. 13th Int Congress Ethnopharmacology Graz 2013.

18 Künstle G, Brenneis C, Haunschild J. 671 Efficacy of Canephron® N against bacterial adhesion, inflammation and bladder hyperactivity. Eur Urol Supplements. 2013;12(1):e671.

19 Nausch B, Künstle G, Mönch B, Koeberle A, Werz O, Haunschild JC. N alleviates pain in experimental cystitis and inhibits reactive oxygen/nitrogen species as well as microsomal prostaglandin E2 synthase-1. Der Urologe. 2015;54:28.

20 Nausch B, Pace S, Pein H, Koeberle A, Rossi A, Künstle G, et al. The standardized herbal combination BNO 2103 contained in Canephron® N alleviates inflammatory pain in experimental cystitis and prostatitis. Phytomedicine. 2019;60:152987.

21 Holler M, Steindl H, Abramov-Sommariva D, Wagenlehner F, Naber KG, Kostev K. Treatment of urinary tract infections with Canephron® in Germany: a retrospective database analysis. Antibiotics (Basel). 2021 Jun 8;10(6):685.

22 Agace W, Hedges S, Andersson U, Andersson J, Ceska M, Svanborg C. Selective cytokine production by epithelial cells following exposure to Escherichia coli. Infect Immun. 1993 Feb;61(2):602–9.

23 Agace WW, Hedges SR, Ceska M, Svanborg C. Interleukin-8 and the neutrophil response to mucosal Gram-negative infection. J Clin Invest. 1993 Aug;92(2):780–5.

24 Mansfield KJ, Chen Z, Moore KH, Grundy L. Urinary tract infection in overactive bladder: an update on pathophysiological mechanisms. Front Physiol. 2022;13:886782.

25 Hannan TJ, Roberts PL, Riehl TE, van der Post S, Binkley JM, Schwartz DJ, et al. Inhibition of cyclooxygenase-2 prevents chronic and recurrent cystitis. EBioMedicine. 2014 Nov;1(1):46–57.

26 Christiaens TC, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract. 2002 Sep;52(482):729–34.

27 Ambite I, Puthia M, Nagy K, Cafaro C, Nadeem A, Butler DS, et al. Molecular basis of acute cystitis reveals susceptibility genes and immunotherapeutic targets. PLoS Pathog. 2016 Oct;12(10):e1005848.

28 Zychlinsky Scharff A, Rousseau M, Lacerda Mariano L, Canton T, Consiglio CR, Albert ML, et al. Sex differences in IL-17 contribute to chronicity in male versus female urinary tract infection. JCI Insight. 2019 May 30;5(13):e122998.