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UTI – quo vadis? New alternatives to treat uncomplicated urinary tract infections

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Abstract

Urinary tract infections (UTI) are one of the most common problems in urology clinics. The European Association of Urology (EAU) has been pioneering in its efforts to disseminate the latest clinical findings through the organization of the annual EAU congresses. At this year's congress (EAU Barcelona 2019), various satellite symposia were organized, focusing on specific issues in the field of urology. "UTI – quo vadis? New alternatives to treat uncomplicated urinary tract infections" was one of the industry-sponsored symposia, organized with the aim of evaluating the current scenario and also throwing light on the paradigm shift in the treatment of acute, uncomplicated lower urinary tract infections (uUTI). Several interlinking topics were presented during this symposium. The topics covered antibiotic resistance, involving a presentation of the current data from the Global Prevalence Study on Infections in Urology (GPIU-study). This discussion was followed by case reports on the impact of antibiotic resistance on the management of patients with UTI/uUTI and treatment options for UTI/uUTI according to current guidelines. The highlight of the symposium was the presentation of very recent data from a gold standard phase III clinical trial (double-blind, double-dummy randomized study), demonstrating the non-inferiority of a herbal medicine (BNO 1045) versus antibiotic therapy (fosfomycin trometamol (FT), as a single dose = 3 g) for the treatment of acute, uncomplicated cystitis.

Keywords: uncomplicated urinary tract infection - uUTI, urinary tract infection - UTI, Canephron, Fosfomycin trometamol, Antibiotic resistance, acute cystitis symptom score - ACSS, global prevalence study on infections in urology - GPIU

Introduction

UTI – Quo vadis? New alternatives to treat uncomplicated urinary tract infections

Symposium organized at the 34th Annual EAU Congress, Barcelona, Spain, 16th of March 2019.

The aim of this symposium was to address the current scenario and to also throw light on the paradigm shift in the treatment of acute, uncomplicated lower urinary tract infections (uUTI). Several interlinking topics were presented during this symposium. The topics covered antibiotic resistance, involving the current data from the Global Prevalence Study on Infections in Urology (GPIU-study) and case reports on the impact of antibiotic resistance on the management of patients with UTI/uUTI and treatment options for UTI/uUTI according to current guidelines. The highlight of the symposium was the presentation of very recent data from a gold standard phase III clinical trial (double-blind, double-dummy randomized study), demonstrating the non-inferiority of a herbal medicine (BNO 1045) versus antibiotic therapy fosfomycin trometamol (FT) for the treatment of acute, uncomplicated cystitis. The speakers were Dr. Zafer Tandogdu (Edinburgh, UK, & Oslo, Norway), Dr. Bela Köves (Budapest, Hungary), Prof. Gernot Bonkat (Basel, Switzerland) and Prof. Florian Wagenlehner (Giessen, Germany). The symposium was chaired by Prof. Kurt G. Naber (Straubing, Germany).

Antimicrobial resistance: role of the global prevalence of infections in urology (GPIU) study in improving therapeutic outcomes

Dr. Tandogdu highlighted antimicrobial resistance as a global clinical concern, even more so in the case of

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urological infections. Health care–associated infections (HAIs), in particular, are associated with high levels of antimicrobial resistance. Health care–associated urogenital tract infections (HAUTIs) are among the most frequently occurring HAIs, with an estimated prevalence of 7–11.0%. The threat level posed by HAUTIs could be dramatic for patients, specifically when looking at morbidity and mortality. The number of surveillance studies conducted in the last century to collect reliable data on HAUTI data is very low. On the other hand, a few prominent studies, such as the EARS-Net study by the European Centre for Disease Prevention and Control (ECDPC), do not specifically monitor urogenital tract infections or urology patients (https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net).

The aspect of antimicrobial resistance (AMR) turning into a health hazard is no longer breaking news. In 2014, Lord Jim O'Neill and his team published a review commissioned by the United Kingdom government entitled, "Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations" (the AMR Review, Fig. 1) [2]. The review estimated that AMR could cause 10 million deaths a year by 2050. The figure of 10 million deaths reported in the AMR review has been debated as this assumption is based on statistical extrapolations, without taking into consideration the real world data. Nonetheless, it has become clear that AMR will be one of the most common causes of death in humans if drastic measures are not taken in the near future [1].

With the purpose of collecting more reliable HAUTI data, the Global Prevalence of Infections in Urology (GPIU) study was initiated in 2003 by the European Section of Infections in Urology (ESIU) and supported by the European Association of Urology (EAU). GPIU is the only multicenter, multinational study started more than 15 years ago that is recording HAUTIs in urology patients worldwide, in an ongoing surveillance protocol that can help to deliver data on adequate empirical antibiotic therapy in hospitalized urology patients according to guideline recommendations.

The primary aims of the study are to evaluate urology practices in terms of hospital infection control and antibiotic consumption practices, and to evaluate the frequency and circumstances of UTIs and surgical site infections in hospitalized urology patients, including the pathogens involved and their antimicrobial resistance [3].

WHO global action plan

Tackling antibiotic resistance is a high priority for the WHO. A global action plan on AMR, including antibiotic resistance, was endorsed at the World Health Assembly in May 2015. The global action plan aims to ensure prevention and treatment of infectious diseases with safe and effective medicines (who.int/news-room/fact-sheets/detail/antibiotic-resistance).

The "Global action plan on antimicrobial resistance" has 5 strategic objectives:

- to improve awareness and understanding of antimicrobial resistance
- to strengthen surveillance and research
- to reduce the incidence of infection
- to optimize the use of antimicrobial medicines
- to ensure sustainable investment in countering antimicrobial resistance

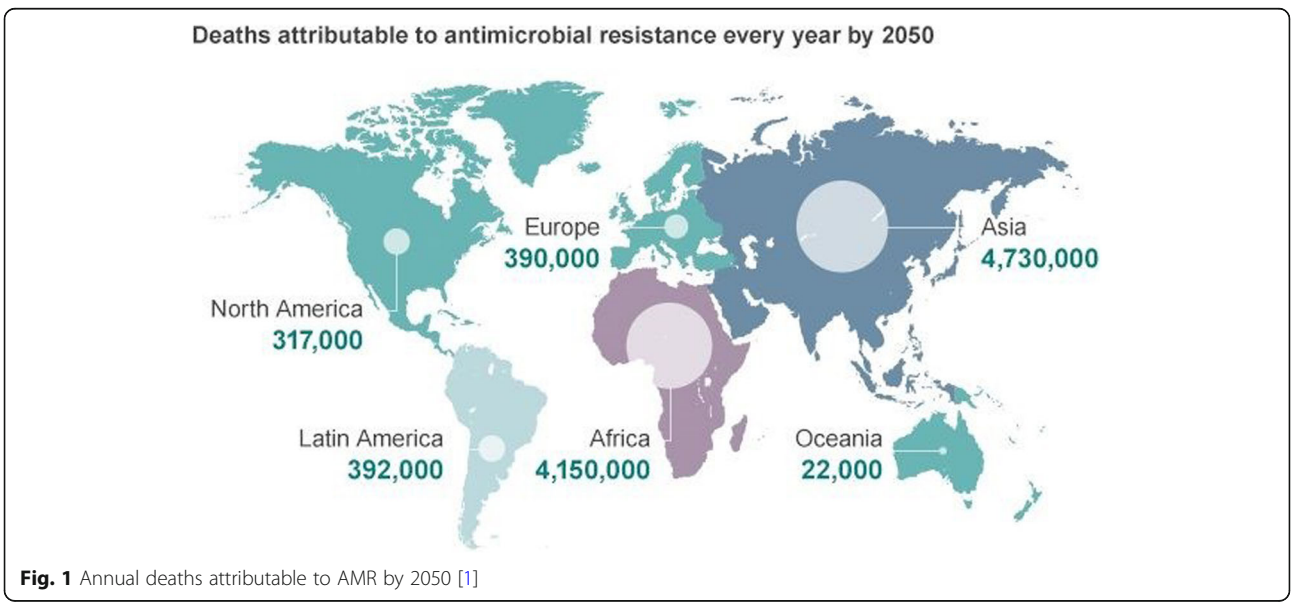

Fig. 1 Annual deaths attributable to AMR by 2050 [1]

Can antibiotic optimization save lives?

Drug-resistant infection rates are approximately 35%, but this can depend on the geographic region and the implementation of local infection control policies. An extrapolation of various parameters has shown an almost 50% mismatch in the case of the disease type and the antibiotic that is used. It is estimated that departments with compliance to infection control policies had 1.5 times more antibiotics available for use in complex infections due to lower resistance rates. Finally, a monitored and guided antibiotic selection improves patient condition in up to 12% of patients. Therefore, drug-resistant infection is a growing problem in the health care environment that requires immediate corrective measures. With ongoing practices, we are less likely to provide the correct antibiotic for the patients if the infection control programs are not complied with and the monitoring information is not being utilized. The GPIU study is an excellent platform, providing support for urologists.

Impact of antibiotic resistance on the management of UTI patients

The magnitude of AMR and its impact on humanity is illustrated by the fact that the World Health Organization (WHO) pronounced AMR to be one of the biggest threats to global health (who.int/news-room/fact-sheets/detail/antibiotic-resistance). The problem of AMR also affects the treatment of patients with UTIs: the rate of UTIs caused by fluoroquinolone-resistant Gram-negative bacteria and multidrug resistant (MDR) organisms is increasing continuously. Consequently, there are a growing number of treatment failures, even in the empirical treatment of community-acquired UTIs. This gives rise to clinical questions, which become more and more relevant in the world of MDR infections. How should we treat an acute episode of lower UTI if it is caused by MDR bacteria and carbapenems are the only effective antibiotics? Do we have any alternatives? What is the best approach to a patient with recurrent asymptomatic bacteriuria caused by an extended-spectrum beta-lactamase (ESBL)-producing pathogen?

Clinical situation: a normal case of recurrent cystitis

A very interesting clinical case, which was presented by Prof. Köves during the symposium, involved a typical 26-year-old woman with recurrent UTI since the start of her sexual activity. She suffered 3–6 episodes per year and was otherwise in a healthy state. The woman was treated by the general practitioner, urologist and gynaecologist, who usually recommended treatment with various antibiotic classes, viz. quinolones, penicillins and cephalosporins. Interestingly, a proper prophylaxis was never considered for this patient. This was certainly counter to the EAU guideline recommendation, which strongly recommends against treating uncomplicated cystitis with aminopenicillins, cephalosporins, and fluoroquinolones.

The therapeutic options that could be considered in such cases are either the use of especially old antibiotics, as recommended within the scope of the EAU guidelines, or treatment with a non-antibiotic therapy. Of course, the non-antibiotic therapy must be supported by sufficient evidence to show its non-inferiority in providing symptomatic relief relative to the antibiotics recommended in the EAU guideline for the treatment of uncomplicated cystitis. A recommendable approach to this therapeutic regimen could be the use of a phytotherapeutic product supported by an adequate level of evidence, e.g. a combination of lovage root, centaury herb and rosemary leaves (BNO 1045) [4].

Prevention strategies which can also lead to a reduction in the number of episodes, as illustrated in this case study, were:

a. increased fluid intake
b. immunoactive prophylaxis
c. vaginal flora regeneration
d. avoiding various risk factors
e. self-treatment with non-antibiotic measures

The results presented for this case demonstrated that the measures yielded a reduction in the number of episodes to only 2–3 episodes per year. Despite the limitation of being a case study, the results clearly demonstrated that appropriate treatment of recurrent UTI episodes is mandatory to avoid MDR. Treatment of acute cystitis caused by ESBL-producing bacteria with guideline-recommended therapeutic options, or by using evidence-based symptomatic non-antibiotic treatment, constitutes a plausible approach.

Can we change our practices in relation to treating acute, uncomplicated cystitis?

Worldwide, UTI is one of the most common indications for antimicrobial prescriptions [5]. Due to the rarity of complications, uncomplicated lower UTIs are considered as benign and self-limiting, with the primary goal of achieving a fast symptomatic relief. The symptoms are bothersome and thus have the potential to drastically impair daily activities and reduce the quality of life [6]. Typical symptoms indicative of acute cystitis may present as frequent urination, urgent urination, burning pain during urination, (sensation of) incomplete bladder voiding after urination, pain in the lower abdomen and visible blood in the urine [7].

Over the past decade, some generally accepted concepts in the field of urology have started to be

questioned. For example, the rather harmful effect of treatment of asymptomatic bacteriuria (ABU) in healthy non-pregnant women not facing selected urological procedures [8] is now accepted and reflected in the guidelines [9]. Furthermore, the bladder environment is no longer believed to be sterile [10, 11].

Recent data now also show that non-antimicrobial treatment may be an appealing therapeutic option and provides an alternative to what is usually first-line antibiotic therapy [4]. But why should we replace antibiotic therapy anyway? Is the patient facing any risk with an alternative? And what options regarding non-antimicrobial therapy can be considered for acute cystitis?

No doubt, appropriate antibiotic therapy has its place in the treatment of UTIs. Unfortunately, treatment also selects for antibiotic resistance in uropathogens and commensal bacteria. Moreover, overuse and misuse hinder antibiotic efficacy in life-threatening events such as urosepsis. Adverse effects of antibiotic use on the gut microbiome and the vaginal flora are generally accepted [12].

Consequently, evolving practices seek to achieve good symptom control for acute, uncomplicated cystitis, while simultaneously reducing antibiotic use. Women who are affected are increasingly aware of issues associated with over- and misuse of antibiotics and are therefore more willing to delay or even skip antibiotic treatment for acute cystitis. Knottnerus et al. [13] reported that over a third of women with UTI symptoms were willing to delay antibiotic treatment when they were asked to do so by their general practitioner. Moreover, the majority of these women reported a spontaneous improvement in the symptoms after 1 week.

Prof. Wagenlehner presented four comparative studies showing that initial treatment with a non-steroidal anti-inflammatory drug (NSAID) can reduce the use of antibiotics in women with uncomplicated UTI (Table 1) [14–17]. Disregarding the pilot trial with small sample size comparing ibuprofen 400 mg TID for 3 days with ciprofloxacin 250 mg BID for 3 days [15], in the three larger studies ibuprofen 400 mg or 600 mg TID for 3 days compared with fosfomycin trometamol (3 g fosfomycin) single dose or with pivmecillinam 200 mg TID for 3 days, respectively, the NSAID showed inferior results to the results obtained with the antibiotics [14, 16]. The same was true comparing diclofenac 75 mg BID with norfloxacin 400 mg BID for 3 days [17]. But in all three studies there was a marked reduction of antibiotic usage. However, the highest reduction in antibiotic use was seen for the multimodal phytotherapy combination of the three plant combination (BNO 1045), with symptomatic relief being comparable in the phytotherapy and antibiotic groups [4].

In the four larger studies [4, 14, 16, 17] in the non-antibiotic treatment arm 5–7 cases per study experienced pyelonephritis as comparted to 0–1 case treated with antibiotics.

Warnings from the past: caution to be exercised in the use of antibiotics in uUTI

Prof. Bonkat, who is a private lecturer at the University of Basel and chair of the European Commission for Guidelines for Urological Infections, presented the treatment options for UTI/uUTI according to the current European international (and national) guidelines. Uncomplicated cystitis is limited to non-pregnant women with no known relevant anatomical or functional abnormalities within the urinary tract or comorbidities [9].

In this particular talk, the warnings from the past were highlighted. The discoverer of penicillin, Alexander Fleming, soon realized not only how useful drugs that have an antibacterial effect are, but also how dangerous a future without them might be, according to his quote “In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted” [18]. From our perspective today, Alexander Fleming was foreseeing the problems associated with multidrug-resistant organisms (MDROs), which are resistant to at least one class of antimicrobial agents. The second issue is that more and more large pharmaceutical companies are announcing their withdrawal from antibiotics research (https://www.businessinsider.de/major-pharmaceutical-companies-dropping-antibiotic-projects-superbugs-2018-7?r=US&IR=T). In fact, the antibiotic pipeline is rather narrow, with few or no novel and innovative new antibiotics and antibiotics for the treatment of diseases commonly caused by antibiotic-resistant bacteria, such as UTI (reactgroup.org/news-and-views/news-and-opinions/year-2018/whats-cooking-in-the-antibiotic-pipeline/).

Clinically proven alternatives to antibiotics in the treatment of uUTI

Prof. Wagenlehner reported on the recently published efficacy study which compared the herbal combination BNO 1045 and single-dose fosfomycin (as fosfomycin trometamol = FT) in female patients with acute lower uncomplicated urinary tract infections. BNO 1045 is a coated tablet containing powdered centaury herb (Centaurii herba) 18 mg, lovage root (Levistici radix) 18 mg and rosemary leaves (Rosmarini folium) 18 mg. The randomized, double-blind, multinational Phase III study in 659 women with acute uncomplicated urinary tract infections (AUC) demonstrated that the phytopharmaceutical BNO 1045 is not inferior to antibiotic therapy with single-shot fosfomycin trometamol (FT) in terms of therapeutic success and reduction of symptoms. The three plant combination with its multimodal activity

Table 1 Overview of clinical studies with symptomatic treatment options (multimodal phytotherapy and NSAIDs) versus antibiotic treatment in uncomplicated lower urinary tract infections

	Wagenlehner et al., 2018 [4]	Gágyor et al., 2015 [14]	Bleidorn et al., 2010 [15]	Vik et al., 2018 [16]	Kronenberg et al., 2017 [17]
Medication	BNO 1045 vs. fosfomycin (FT)	Ibuprofen vs. fosfomycin	Ibuprofen vs. ciprofloxacin	Ibuprofen vs. pivmecillinam	Diclofenac vs. norfloxacin
Study design[a]	Double-blind, controlled, double-dummy, parallel group, randomized, multicentre, multinational Phase III	Double-blind, randomized, multicentre, comparative effectiveness trial with two parallel active treatment arms	Double-blind, randomized, controlled equivalence trial	Double-blind, randomized, parallel-group, multicentre, non-inferiority trial	Double-blind, randomized, controlled non-inferiority trial
Inclusion criteria[b]	Sum score of the three main uUTI symptoms (dysuria, pollakiuria and urgency) reported on the ACSS-typical domain on Day 1 is ≥6, leukocyturia on Day 1, confirmed by positive dipstick	Dysuria and/or frequency/urgency of micturition, with or without lower abdominal pain	At least one of the main UTI symptoms, dysuria and frequency	Dysuria combined with either increased urinary frequency or urinary urgency, or both, with or without visible haematuria	One or more symptoms of acute lower UTI (dysuria, frequency, macrohaematuria, cloudy or smelly urine) or self-diagnosed symptomatic cystitis in combination with a positive urine dipstick test for nitrite or/and leucocytes
Exclusion criteria[b]	History of recurrent infection of the urinary tract	UTI within the past 2 weeks	UTI within the last 2 weeks	Symptoms of UTI within the last 4 weeks	Recurrent UTI (> 3 infections during the past 12 months)
Age	18–70	18–65	18–85	18–60	18–70
Number of patients	$n = 325$ (BNO 1045), $n = 334$ (FT)	$n = 241$ (ibuprofen), $n = 243$ (FT)	$n = 40$ (ibuprofen), $n = 39$ (ciprofloxacin)	$n = 194$ (ibuprofen), $n = 189$ (pivmecillinam)	$n = 133$ (diclofenac), $n = 120$ (norfloxacin)
Location	Multinational	Germany	Germany	Multinational	Switzerland
Duration in days	1–38	0–28	0–28	0–28	0–30
Dosage and duration of administration	BNO 1045, 7 days, 2 tablets TID Fosfomycin trometamol (FT), single dose on Day 1 (3 g)	ibuprofen, 3 days, 1 tablet (400 mg) TID fosfomycin trometamol (FT), single dose on Day 1 (3 g)	ibuprofen, 3 days, 1 tablet (400 mg) TID ciprofloxacin, 3 days, 1 tablets (250 mg) BID	ibuprofen, 3 days, 1 tablet (600 mg) TID pivmecillinam, 3 days, 1 tablet (200 mg) TID	diclofenac, 3 days, 1 tablet (75 mg) BID norfloxacin, 3 days, 1 tablet (400 mg) BID
Paracetamol	Allowed	Not reported	Not reported	At patients' discretion. There is the possibility that intake of paracetamol may have masked symptomatic progression of upper UTI.	Not reported
Visits/calls* (days)	1,4*,8,38	1*,3*,5*,7*,28	0, 4, 7, 28	?	30*
Symptom scale	ACSS questionnaire: Mean sum scores of the ACSS-typical domain between Days 1 and 38 Typical symptoms ($n = 6$) of lower uUTIs (ACSS-typical), where 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms	Dysuria, frequency/urgency of micturition, and low abdominal pain, each on a five point scale from 0 to 4.	Intensity of main symptoms - dysuria, frequency, low abdominal pain - was recorded, scoring each symptom from 0 (none) to 4 (very strong)	Patient diary for recording daily symptoms, diary was based on a previously validated version	The self-report questionnaire used to ascertain the severity of symptoms was developed based on questionnaires described by Clayson et al. and Little et al. 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 to 10 in a diary and on day

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					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. Complete absence of symptoms was defined as 0 points on all components.
Primary endpoint(s)	Additional antibiotic intake between days 1–38	Total number of courses of antibiotics on days 0–28, burden of symptoms on days 0–7 as area under the curve	Symptom resolution on day 4	Proportion of patients who felt cured by day 4, as assessed based on a patient diary	Resolution of symptoms at day 3 (72 h after randomization and 12 h after intake of the last study drug)
Secondary endpoints[b]	ACSS questionnaire assessments at days 4, 8 and 38	Numbers of adverse events	Burden of symptoms on days 4 and 7 (based on the sum score of all symptoms), symptom resolution on day 7 and frequency of relapses	Proportion of patients in need of secondary treatment with antibiotics and cases of pyelonephritis	Use of any antibiotic (including norfloxacin and fosfomycin as trial drugs) up to day 30 (ITT)
Statistics	Non-inferiority margin (− 15%)	Superiority in the first and non-inferiority (125%) in the second co-primary endpoint	Rough estimate of equivalence of ibuprofen and ciprofloxacin for uUTI regarding symptom resolution		Non-inferiority margin (−15%)
Main Result	Antibiotic Reduction of 85%. Non-inferiority demonstrated. Clinical benefit on reduction of the main ACSS-typical symptoms was observed after 3 days of treatment. More cases of pyelonephritis in the non-antibiotic group.	Fosfomycin: 243 study antibiotic + 34 additional for UTI. Ibuprofen: 81 additional for UTI -- > Antibiotic Reduction of 67%. Symptom burden sum score decreased in both groups (Day 0: 6 -- > Day 7: < 1) -- > non-inferiority margin of 125% exceeded. Higher burden of symptoms. More cases of pyelonephritis in the non-antibiotic group.	Assumption of non-inferiority is supported, but confirmation by further trials needed.	Ibuprofen was inferior to pivmecillinam for treating uUTI, reducing the use of antibiotics came at the cost of stronger symptom burden, longer duration of symptoms, and more complications.	Diclofenac is inferior to norfloxacin for symptomatic relief in UTI and is likely to be associated with an increased risk of pyelonephritis.
Symptoms	Symptom decline comparable in both groups (statistical significance in favour of fosfomycin on Day 4)	Symptoms lasted 1 day longer in the ibuprofen group. Day 4: 56% in fosfomycin group symptom-free vs. 39% in the ibuprofen group.	As for symptom resolution, 58.3% of patients in the ibuprofen group and 51.5% in the ciprofloxacin group were completely free of symptoms on Day 4 (difference non-significant). On Day 7, the proportion of symptom-free patients had increased further in both groups, without a significant difference between groups. The course of symptoms in	Patients in the pivmecillinam group generally felt cured sooner than the patients in the ibuprofen group. The median duration of symptoms was 6 days in the ibuprofen group and 3 days in the pivmecillinam group.	The median time until resolution of symptoms was 4 days in the diclofenac group, compared with 2 days in the norfloxacin group.

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	Wagenlehner et al., 2018 [4]	Gágyor et al., 2015 [14]	Bleidorn et al., 2010 [15]	Vik et al., 2018 [16]	Kronenberg et al., 2017 [17]
			terms of mean symptom sum scores: with respect to Day 4, the difference in total sum scores was − 0.33 score points (95% CI (− 1.13; + 0.47)) in the PP analysis (primary analysis). The corresponding ITT analysis resulted in a difference of 0.50 (95% CI: (− 1.31; + 0.31). With regard to general impairment, there were no significant differences between the ibuprofen and ciprofloxacin groups. In particular, no difference could be shown between groups for the course of dysuria.		
Safety	5 cases of pyelonephritis (BNO 1045) vs. 1 case (fosfomycin)	5 cases of pyelonephritis (ibuprofen) vs. 1 case (fosfomycin) One gastrointestinal haemorrhage in the ibuprofen group	58 non-serious adverse events (32 ibuprofen, 26 ciprofloxacin)	7 SAEs during the trial, 1 in the pivmecillinam group and 6 in the ibuprofen group. 5 patients developed a febrile UTI and 7 patients developed pyelonephritis, all initially treated with ibuprofen	6 cases of pyelonephritis (diclofenac) vs. 0 (norfloxacin)
Recurrence	The AB rates were comparable across the different reasons for additional AB intake during the clinical trial (persistent or worsening symptoms: BNO 1045: 66.0% and FT: 67.7%; recurrent symptoms: BNO 1045: 23.4% and FT: 25.8%; no symptoms reported: BNO 1045: 10.6% and FT: 6.5%).	Comparable in both groups, but significant more recurrences after day 14 in the FT group (11% vs. 6%)	The surprisingly high number of patients presenting again with persistent/recurrent symptoms while taking ciprofloxacin (18%) might indicate that antibiotic treatment takes a few days to resolve symptoms, a fact which may have worried trial patients who did not know which drug they were taking.	Comparing the subgroup with recurrent UTIs (i.e., 3 or more UTIs during the previous 12 months) to the subgroup with 0 ± 2 UTIs within the last 12 months, the highest symptom burden over 6 days was observed in the recurrent UTI patients treated with ibuprofen. The difference in symptom burden between the treatment groups was greater for those with recurrent UTIs, but significant in both subgroups.	Recurrent UTI: 4% diclofenac vs. 3% norfloxacin 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.
Limitations	Microbiological data (but not mandatory for uUTIs)	Inclusion was biased towards patients with less severe symptoms -- > results only applicable to patients with mild to moderate symptoms, rather than all uUTI Neither symptom score or measurement of the area under the curve were validated -- > relevance for affected patients was not formally proved	Small sample size, pilot trial	High dosage of ibuprofen, low dosage of pivmecillinam	Rescue antibiotic (fosfomycin) could be taken at patients' discretion after day 3 Symptom resolution ≠ complete absence of symptoms
Conclusion	Trial may inform treatment choices	Non-inferiority not achieved,	Results support the assumption of	Until we can identify those women	Trial failed to detect non-inferiority

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	and encourage wider adoption of antibiotic alternatives, such as BNO 1045, for the treatment of lower uUTIs in routine clinical practice	no general recommendation of the "ibuprofen first approach"	non-inferiority, but further trials or an adequately powered trial is necessary.	in need of antibiotic treatment to prevent complications, ibuprofen alone cannot be recommended to women with uUTIs.	of NSAIDs compared with antibiotics for symptom control. Symptomatic treatment of lower urinary tract infections prolongs symptom duration and is likely to be associated with an increased risk of pyelonephritis.

[a]As reported in the publication
[b]Not a complete list

represents a useful symptomatic treatment option. Anti-inflammatory [19], analgesic [20], spasmolytic [21] and anti-adhesive effects [19] have been demonstrated in various preclinical in vivo and in vitro studies for this unique combination of three medicinal herbs.

Finally, the transfer of these pharmacological effects into clinical benefits is reported in this randomized, controlled, double-blind, double-dummy, multicentre, multinational Phase III study, including 659 women aged 18–70 years with the typical symptoms of newly diagnosed acute uncomplicated cystitis [4]. Patients in the BNO 1045 group received 7 days 2 tablets of BNO 1045 TID plus a single dose of FT-matched placebo and patients in the FT group received a single dose of FT plus 7 days of BNO 1045-matched placebo (= double-dummy design). After the treatment period, there was a 30-day follow-up period. The primary endpoint was the non-inferiority of BNO 1045 versus FT with regard to the need for additional antibiotic therapy during the study period (days 1–38).

83.5% of patients in the BNO 1045 group and 89.8% of patients in the FT group required no additional antibiotic therapy. Thus, the three plant combination was not statistically inferior to the antibiotic FT in the treatment of acute, uncomplicated cystitis with regard to the primary endpoint ($\Delta = -6.3\%$, lower limit of the confidence interval: -11.99%, $p = 0.0014$). The symptom decline (measured using the "acute cystitis symptom score", ACSS [22] as the sum score for the "typical" symptoms) was comparable in both groups during the study period. The herbal therapy was well tolerated.

Thus, BNO 1045 serves as an evidence-based efficacious substitute to antibiotics for the treatment of acute uncomplicated cystitis in women and helps to reduce the outpatient use of antibiotics to a significant extent. This is of major importance in the context of the antibiotic stewardship strategy, in order to rationalize the wide-spread use of antibiotics and the ensuing danger of antibiotic resistance (who.int/news-room/fact-sheets/detail/antibiotic-resistance).

Conclusion

As one of the most common bacterial infections, UTIs have not only a large individual, but also socio-economic importance, particularly affecting women. Primarily, antibiotic therapy is recommended, which however is linked to development of resistance and damage of the natural microbiome. A critical revaluation of antibiotic usage and intensive search for alternatives, which also corresponds to the wishes of many women, has led to considerations of solely symptomatic therapy of acute lower uncomplicated infections. Recent studies with NSAIDs have reported a significant reduction in the use of antibiotics in symptomatic initial treatment, but with a higher incidence of symptoms. A new clinical study has shown that the three-plant combination of rosemary, centaury and lovage is not inferior to fosfomycin in terms of therapeutic success. Moreover, also the symptom reduction reported with a validated score was on a comparable level. This trial may encourage wider adoption of evidence-based antibiotic alternatives for the treatment of lower uUTIs in routine clinical practice reducing widespread antibiotic use.

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Authors' contributions
KGN had the lead in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
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Ethics approval and consent to participate
Not applicable; this is a review article.

Consent for publication
Not applicable; this is a review article.

Competing interests
KGN reports personal fees from Adamed, Apogepha, Aristo, Biomerieux, Bionorica SE, Daiichi Sankyo, Enteris Biopharma, Eumedica, GlaxoSmithKline, Gruenenthal Mexico, Helperby Therapeutics, Hermes, Medice, Meiji Seika Pharma, MerLion, MSD Sharp & Dohme, OM Pharma and Vifor, Paratek, Roche, Rosen Pharma, and Zambon.
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