BJU Int 2022; **129:** 668–678 doi:10.1111/bju.15630

BJUI
BJU International

Review

Management of uncomplicated recurrent urinary tract infections

Mary Zare[1], Maria J.G.T. Vehreschild[1] and Florian Wagenlehner[2]

[1]*Department of Internal Medicine, Infectious Diseases, University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt am Main, and* [2]*Department of Urology, Pediatric Urology and Andrology, Justus Liebig University of Giessen, Giessen, Germany*

Objectives

To discuss optimal management of recurrent urinary tract infections (UTIs) in women. About every second woman experiences at least one UTI in her lifetime, of those 30% experience another UTI, and 3% further recurrences. Especially young healthy women without underlying anatomical deficiencies suffer from recurrent UTIs (rUTI), which are associated with significant morbidity and reduction in quality of life.

Methods

This is a narrative review, investigating publications dealing with recurrent UTI in women. Risk factors and options for management are discussed.

Results

The increased susceptibility of women to rUTI is based on the female anatomy in addition to behavioural, genetic, and urological factors. However, why some women are more likely than others to develop and maintain rUTI remains to be clarified. Invasive characteristics of certain uropathogenic *Escherichia coli* that are able to form extra- and intracellular biofilms and may therefore cause delayed release of bacteria into the bladder, may play a role in this setting. Treatment recommendations for an acute episode of rUTI do not differ from those for isolated episodes. Given the nature of rUTI, different prophylactic approaches also play an important role. Women with rUTI should first be counselled to use non-antibiotic strategies including behavioural changes, anti-adhesive treatments, antiseptics, and immunomodulation, before antibiotic prophylaxis is considered. In addition to the traditional treatment and prophylactic therapies, new experimental strategies are emerging and show promising effects, such as faecal microbiota transfer (FMT), a treatment option that transfers microorganisms and metabolites of a healthy donor's faecal matter to patients using oral capsules, enemas, or endoscopy. Initial findings suggest that FMT might be a promising treatment approach to interrupt the cycle of rUTI. Furthermore, bacteriophages, infecting and replicating in bacteria, have been clinically trialled for UTIs.

Conclusion

Due to the limitation of available data, novel treatment options require further clinical research to objectify the potential in treating bacterial infections, particularly UTIs.

Keywords

recurrent urinary tract infections, diagnostic algorithm, preventive strategies, faecal microbiota transfer, bacteriophages

Definition and Categorisation

Urinary tract infections (UTIs) are the most frequently diagnosed type of infection in the outpatient setting, mostly affecting women [1,2]. The individual burden of disease is considerable, given the nature of associated symptoms which regularly leads to restrictions in everyday life and a consecutive negative impact on mental health, especially in cases of recurrent UTIs (rUTIs) [3,4]. From a societal perspective, the economic burden of disease, as well as the considerable potential for development of antibiotic resistance need to be recognised. While the impact on each individual patient may be limited, the overall incidence of UTIs results in a high impact at the population level [4,5].

Recurrent UTIs are defined as two or more symptomatic episodes within 6 months or three or more symptomatic

episodes in a timeframe of ≤12 months. From a pathophysiological point of view, a rUTI may present as a relapsing infection that corresponds to an incomplete clearance of the causative pathogen and occurs within 14 days of completion of treatment or as a re-infection presenting after 14 days of treatment completion. In the latter case, a new urine culture should be obtained. Overall, 90% of recurrences are classified as re-infections [6,7].

Epidemiology

About every second woman experiences at least one UTI in her lifetime, but prevalence differs considerably by age group. For instance, young women represent a high proportion of patients with a prevalence of 8% for women aged <20 years and 12% for women aged 20–29 years [5,8]. This peak may be explained by the comparatively higher sexual activity in this specific subgroup, which is considered a major risk factor for UTIs. For middle-aged women (aged 35–65 years) a decrease of UTIs is observed with rebounding numbers for women aged >65 years who have entered menopause. The prevalence in elderly women is roughly 20%, compared to 7% for the overall population, making this subgroup particularly vulnerable to UTIs [2,5]. Roughly, 30% of patients with UTIs experience a recurrence, and ~3% suffer from further recurrences, which severely affect patients' quality of life [3,4]. Recurrent UTIs are common among young women, even when no underlying anatomical or physiological abnormalities can be identified.

Pathophysiology and Risk Factors

Women are considered more vulnerable to UTIs than men, due to the urethra's proximity to the anus, which ensues in a distinct microbiome in the periurethral area and allows pathogens from the faecal reservoir, such as uropathogenic *Escherichia coli* (UPEC), an easier access to the bladder and renal pelvises. In addition, the female urethra is shorter than the male, further facilitating ascendance of pathogens into the bladder [9,10]. Besides being female, further host-related risk factors for rUTIs have been identified, including behavioural, genetic, and urological factors. Especially in young healthy women, sexual intercourse has been identified as a key risk factor. Particularly the frequency of intercourse, frequent partner changes, and the use of diaphragms or spermicides are linked to the occurrence of rUTIs [11]. In addition to sexual activity, further risk factors include early onset of UTI episodes and having a mother with a history of UTIs [12]. The potential relevance of genetics is further underlined by the finding that certain blood groups have been linked to an increased susceptibility to rUTIs. The affiliation to Lewis-non-secretor phenotypes has been associated with an increased predisposition to rUTIs, mediated by an increased adherence of uropathogens to the urothelial membrane by expression of unique globoseries-glycolipid-receptors [13].

Oestrogen deficiency leads to a microbiome shift, favouring more pathogenic bacteria and anatomical and functional urological factors may play an important role after menopause. Urinary incontinence, identification of a cystocele and post-voiding residual urine have been discussed controversially as risk factors for rUTI [14].

Faecal and Urinary Reservoir

Approximately 80% of uncomplicated UTIs are caused by UPEC, which show increased adherence to vaginal epithelial and urothelial cells [6,10]. Different factors contribute to the predominance of UPEC in causing UTI. They are able to form a biofilm that acts as a barrier against the diffusion of antibiotics [10]. They can substantially downregulate their metabolism and thus escape most antibiotic mechanisms of action. UPEC are also capable of invading urothelial cells and building biofilms inside the cells; thus, hiding from the host immune response. Although out of reach for the immune system, the pathogen is still able to trigger symptoms and is not detected by diagnostic tools, impeding the application of targeted therapeutic strategies. It has been claimed that intracellular UPEC can be released through the exfoliative action of *Gardnerella vaginalis*, a physiological component of the vaginal and bladder microbiota; thus, triggering episodes of rUTI [20]. The epithelial exfoliation caused by *G. vaginalis* also facilitates invasion of UPEC into deeper layers of the bladder wall; thus, maintaining a vicious inflammatory cycle. This hypothesis is indirectly supported by a study, which showed, that 77% of analysed rUTIs were caused by UPEC-strains that had also been isolated during the initial UTI episode [6,15].

Further pathogens commonly causing uncomplicated UTIs include *Proteus mirabilis*, *Klebsiella pneumoniae* and other Enterobacteriaceae. As they are part of the physiological faecal reservoir, it is not surprising that 95% of all UTIs are caused by the ascension of pathogens from the urethra to the bladder [1,6]. This is supported by a study analysing faecal and vaginal samples from patients with UTIs in comparison to healthy controls. Data showed that 87% of patients carried the pathogen causing the UTI within their faecal microbiota, suggesting the influential role of the faecal reservoir in the pathogenesis [16].

Until recently, it was assumed that potential pathogens from the faecal reservoir ascended into the bladder as a sterile environment. This assumption has been questioned, as a physiological bladder microbiota has been identified by several authors [17,18]. For the bladder microbiome, the highest abundance in samples was shown for Lactobacilli, which also contribute to the characteristic vaginal microbiota with its relatively acidic pH. It can be hypothesised that the presence of these bacteria in the bladder might also have a protective effect with respect to UTI susceptibility [19].

Diagnostic Evaluation

The overall management of UTI from an acute episode to prophylactic measures in case of rUTIs is shown in Fig. 1. The routine diagnostic evaluation for rUTIs differs markedly between different disciplines. Whilst sometimes no examinations are performed, not even urine sampling, in other areas, especially in urology an extensive evaluation including cystoscopy and X-ray is performed.

A study investigating the current practice of diagnostic evaluation in recurrent cystitis, was performed in the Netherlands, evaluating the clinical relevance of the outcome of various diagnostic procedures in young women referred for recurrent cystitis [20]. In essence, the study revealed that the yield of extensive and invasive diagnostic procedures, although frequently performed amongst urologists, is low [20].

There is a guideline consensus that urine analysis including urine culture should be performed in the diagnostic evaluation of recurrent cystitis, and that an extensive evaluation (e.g. cystoscopy, X-ray) in women aged <40 years and no obvious risk factors should not be performed routinely [21]. However, it should be performed in atypical cases, e.g. if urolithiasis, obstructed voiding, interstitial cystitis, or urothelial carcinoma is suspected [21].

In addition, the possible and sometimes age-related risk factors should be taken into account and actively inquired or investigated. Especially in children, elevated post-void residual urine predicts rUTI [22]. The focus in the diagnostic evaluation should be mainly directed toward behavioural aspects and should also include a fluid intake and voiding diary, and perhaps uroflowmetry [20,21].

In addition, a nomogram has been established, accurately (0.85 concordance index) predicting the risk probability for recurrent cystitis within 1 year in women after an episode of UTI. This nomogram includes six variables, such as the number of sexual partners, the bowel function, the type of pathogens isolated (if Gram-positive or -negative bacteria were isolated), the hormonal status, the number of previous UTI recurrences, and if there was a previous treatment of asymptomatic bacteriuria [23]. This nomogram assists in identifying women at high risk of symptomatic recurrence. Those women would then be candidates for prophylaxis strategies. While such a nomogram can be helpful in the early identification of women at risk of rUTI, its concrete clinical consequence is still limited at this point. However, nomograms are important tools in the design of future trials for the prevention of rUTI.

Finally, the role of novel next-generation diagnostic approaches should be discussed. Based on the results of 16s ribosomal RNA sequencing and metagenomic shotgun sequencing in combination with expanded urinary culture, the notion of a physiologically sterile urinary bladder environment was challenged over the last years, and the presence of a specific bladder microbiome was proposed. In a head-to-head phase II study symptomatic improvement was significantly better in patients where treatment was based on next-generation sequencing results, compared with conventional culture testing alone [24]. Nevertheless, the difficulty in interpreting the results yielded by these techniques does not yet permit their integration into routine diagnostics.

Antibiotic Treatment of an Acute Episode of rUTI

To provide context for the treatment of rUTI, we will give a short overview on the treatment on non-recurrent uncomplicated UTI. Recommended fist-line antibiotic drugs include nitrofurantoin, fosfomycin trometatmol and pivmecillinam, according to international guidelines [25,26]. Trimethoprim/sulfamethoxazole are recommended to be used in areas with known *E. coli* resistances <20%. Other than that, second-line treatment options include cephalosporins. Of note, the treatment duration is recommended to be short-termed, usually in the range of 1–5 days. An overview of the antibiotic treatment options are presented in Table 1.

In general, treatment recommendations for an acute episode of rUTI do not differ from those for isolated episodes as described above. To further limit resistance development in this setting, management of acute episodes by use of increased fluid intake and non-steroidal anti-rheumatic (NSAR) drugs can be encouraged, if the patient is an otherwise healthy woman with mild symptoms and no risk factors for a severe course of disease, e.g. immunosuppression or an underlying urological condition [27]. The efficacy of NSARs has been evaluated in a randomised controlled trial (RCT), where 248 women with acute uncomplicated UTI were treated with ibuprofen (400 mg, three-times a day) compared to 246 women treated with fosfomycin (3 g, single dose). Two-thirds of the women treated with ibuprofen recovered from the UTI, not requiring antibiotic treatment. However, the symptomatic burden was higher in the NSAR-group as well as the occurrence of pyelonephritis (2% vs 0.4%, $P = 0.12$). The results of this RCT might suggest the beneficial effect of NSAR in mild-to-moderate symptomatic UTIs; however, the application should be recommended carefully [28]. In addition phytotherapy, such as BNO 1045 [29] or Uva Ursi [30] has also been investigated in RCTs suggesting non-antibiotic treatment efficacies of 83.5% and 63.6%, respectively. A retrospective database analysis has also shown that treatment of the acute phase of cystitis with BNO 1045 results in less recurrent UTI [31].

Fig. 1 Flowchart of prophylactic strategies in the prevention of recurrent UTI.

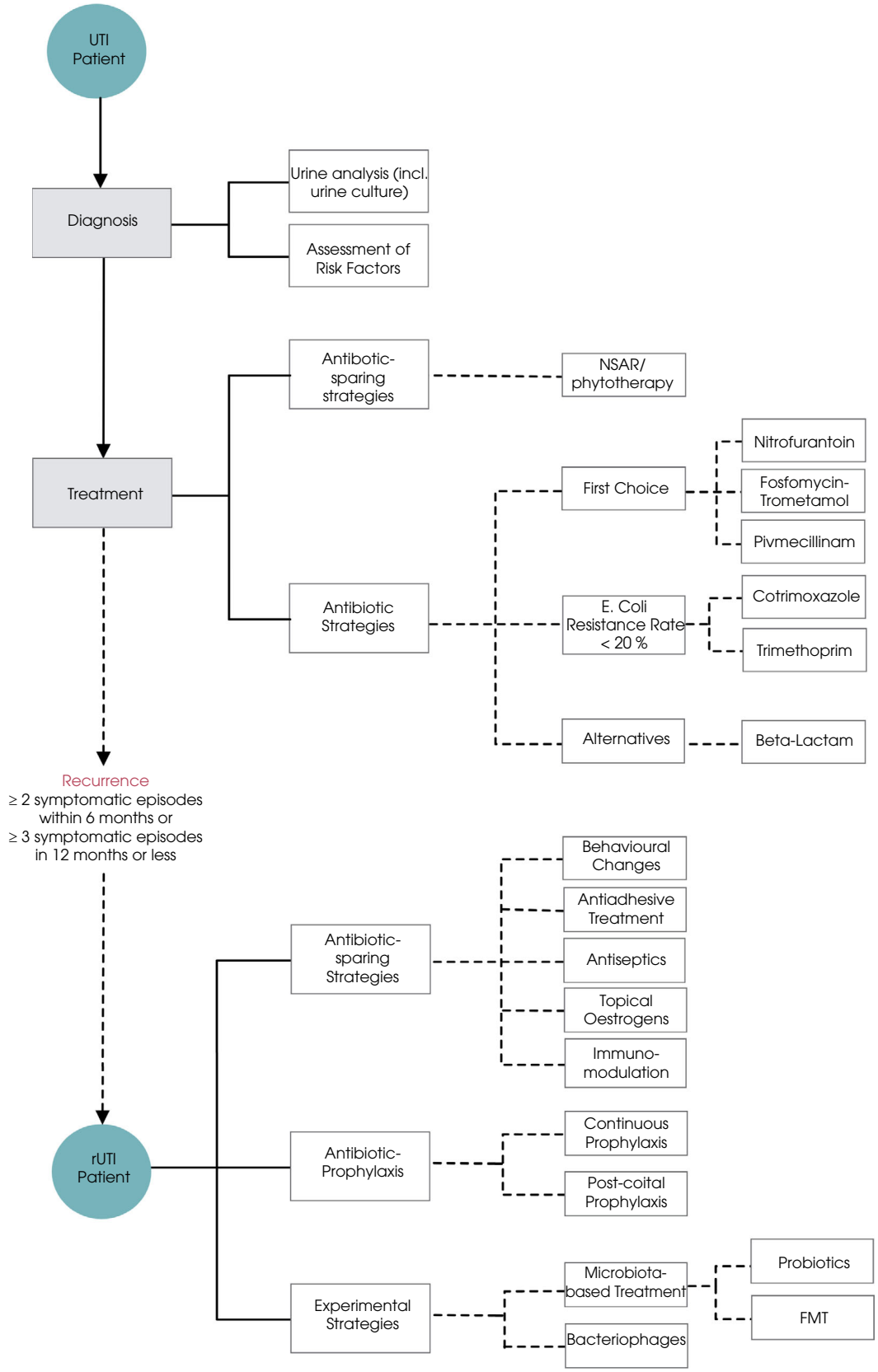

Table 1 Antibiotic treatment recommendations [25,26].

	Antibiotic	Dosage, mg	Regimen	Duration, days
First choice	Nitrofurantoin macrocrystal prolonged release	100	Twice a day	5
	Fosfomycin trometamol	3000	Once	Once
	Pivmecillinam	400	Thrice a day	3–5
As first choice in areas with resistance rates for *E coli* of <20%	Trimethoprim/sulfamethoxazole	160/800	Twice a day	3
	Trimethoprim	200	Twice a day	5
Alternatives	Cefadroxil	500	Twice a day	3

Resistance development may further be limited by shortened treatment regimens; however, there are few studies assessing this particular aspect of treatment. A recently published randomised trial including 254 men with UTI found a 7-day treatment regimen with ciprofloxacin or trimethoprim/sulfamethoxazole non-inferior to a 14-day regimen [32]. While these findings are not directly transferable to infections in women, they suggest that assessment of shorter treatment durations may still harbour significant potential for exposure to antibiotics in different associated indications.

Concerning the treatment of complicated UTI caused by multidrug-resistant organisms, some valuable additions have been made to the antibiotic armamentarium in recent years. Ceftolozan-tazobactam covers a broad range of Gram-positive and -negative bacteria, including extended spectrum β-lactamase (ESBL)-carrying Enterobacteriaceae and *Pseudomonas* spp. Ceftazidime-avibactam further adds to this spectrum through its coverage of a broad range of carbapenemase-producing bacteria. Finally, cefiderocol, the first registered siderophore-cephalosporin and plazomicin, a next-generation aminoglycoside, add the coverage of *Acinetobacter* spp. to this spectrum. Another novel antibiotic with particular relevance to the treatment of UTIs is temocillin. While providing broad coverage of typical Gram-negative uropathogens, including ESBL-producing strains, it has only limited impact on the physiological microbiota; thus, reducing the selection of multidrug-resistant organisms and other typical antibiotic-associated side-effects.

In women with long-term rUTI who have developed a profound understanding of their symptoms and have shown to be compliant to medical instructions in the past, the option of self-treatment can be useful in cases were access to medical care may be temporarily limited, e.g. during travel. However, patients should be instructed to present with a physician, if symptoms do not improve significantly within 48 h after initiation of self-treatment [33,34].

Prevention of rUTI Using Non-Antibiotic Strategies

For long-term preventive measures, guidelines recommend an extensive consultation regarding available behavioural options and other prophylactic strategies. Before antibiotic prophylaxis is considered, alternative strategies should be exploited as far as possible, even though the basis of evidence for many of these strategies may often be limited [25,26].

Behavioural Changes

The increased intake of fluids is a commonly discussed strategy. The suggested mechanism of action is the evacuation of pathogens by rinsing of the bladder and urethra. On the other hand excessive fluid intake might dilute the naturally present anti-bacterial substances such as the Tamm-Horsfall-protein or cathelicidin [35]. In a randomised trial, it was, however, confirmed that increased water intake in patients drinking <1.5 L of fluid daily is an effective strategy to prevent recurrent cystitis in premenopausal women [36].

Sexual activity is also linked to the onset of UTIs and especially anal intercourse is being discussed as a trigger of rUTI and may therefore be discouraged in affected patients [37]. In addition, contraception using condoms, diaphragms or intrauterine devices covered with spermicides such as nonoxynol significantly increases the risk of rUTIs [38].

Finally, hypothermia has been linked to the occurrence of rUTI. A study exposed 29 patients to hypothermia for 55 h, by cooling their feet. Six of these women showed symptoms of UTIs, whereas no further episodes of UTI were reported in the control time period [39]. Thus, patients suffering from rUTI should be advised to avoid hypothermia.

Anti-adhesive Treatments

Cranberry products, available in different preparations are a traditionally popular method to prevent rUTI. From a mechanistic point of view, a protective effect seems possible, as *in vitro* studies demonstrated inhibition of adhesion of uropathogens to uroepithelial cells [40]. Unfortunately, clinical trials assessing the protective efficacy of cranberry products are usually limited by their size, a lack of blinded control groups and other trial design issues [41-43]. Even meta-analyses come to different conclusions on the clinical efficacy of cranberry products [44,45]. Furthermore, the pharmaceutical form and dosage vary significantly between trials, such that it remains difficult to recommend a specific

product or dosage over another. Nevertheless, as the likelihood of side-effects is limited, besides minor gastrointestinal symptoms and a potentially increased caloric intake, patients wanting to try cranberry products should not necessarily be discouraged.

Another anti-adhesive agent is D-mannose, which is orally administered and generally well tolerated. The mechanism of action is based on the saturation of bacterial adhesion structures, such as pili and adhesins; thus, preventing pathogen adhesion to the bladder surface [46]. A RCT of moderate size showed efficacy rates comparable to antibiotic options like nitrofurantoin, therefore presenting a potential safe and effective alternative [47].

Glycosaminoglycan (GAG)-layer substituents are anti-adhesives that are administered via instillation into the bladder. GAG reduce bacterial adhesion by restoring damaged mucosal surfaces of the bladder and thus preventing pathogen adhesion. Studies reported UTI-frequency reduction under GAG-treatment from 4.99 to 0.56 episodes/year ($P < 0.001$) and in another study from 4.3 to 0.3 episodes/year ($P < 0.001$) [48,49]. Furthermore, one study showed a reduction of the absolute risk of rUTIs of 77% at 12 months of follow-up in 28 patients, compared to the placebo group (29 patients), with no reported serious adverse events [48].

Antiseptics

Another popular prophylactic method is the regular usage of urogenital disinfectants, e.g. chlorhexidine or iodine liquids. The suggested mechanism of action is the early eradication of potential pathogens. However, there is no sufficient evidence supporting the application of urogenital disinfectants in general. Furthermore, excessive intimate hygiene can disturb the physiological vaginal microbiota and its associated colonisation resistance to potential uropathogens [50].

In addition to local disinfectants, the oral intake of methenamine was evaluated by a RCT to compare its preventive efficacy to that of an antibiotic prophylaxis with trimethoprim. Patients received either methenamine or trimethoprim for ≥6 months; outcomes were evaluated 12 months after initiation of prophylaxis. Overall, 65% of patients in both treatment groups (28/43 in the methenamine group, 30/46 in the trimethoprim group) experienced UTI recurrences ($P = 0.98$); thus, showing similar efficacy in the prophylaxis of rUTI [51].

In addition, several plant-based disinfectants for oral application as tablets, capsules or tea are available. One prominent representative are the leaves of *Arctostaphylos uva-ursi*, commonly known as bearberry. A clinical trial analysed the effect of bearberry leaves and dandelion roots for 30 days vs placebo in 57 patients with rUTI. After 12 months, none of the patients in the treament group had suffered from recurrences, whereas in the placebo group 23% (five of 27) of patients experienced another episode of rUTI [52]. Yet, the intake of bearberry leaves should be limited due to possible quantity-dependent side-effects [50].

Another plant-based preparation, consisting of nasturtium herbs (*Tropaeoli majoris herba*) and horseradish roots (*Armoraciae rusticanae radix*) was evaluated in a trial that randomised 174 patients to treament or placebo for 90 days and a follow-up of 12 months. There was no significant difference in the intention-to-treat. In the per-protocol population, the mean number of rUTIs was 0.43 vs 0.77 ($P = 0.035$) [53].

Topical Oestrogens

Two smaller trials have shown the efficacy of vaginal oestrogen preparations in reducing the incidence of rUTI in postmenopausal women [54,55]. The mechanism of action is believed to be the positive impact of oestrogen on the vaginal microbiota. In the larger one of these trials, 108 patients were randomised to receive a vaginal oestrogen ring or placebo over a period of 36 weeks. Another episode of rUTI occurred in 51% and 80% of patients, respectively. In another trial, 171 postmenopausal women with rUTI were randomised to receive vaginal oestrogen or daily nitrofurantoin prophylaxis, the latter approach was more effective in preventing infections with 2 and 0.8 UTI episodes/patient-year ($P < 0.001$). However, the limited protective efficacy of oestrogen preparations in this study may be a result of the comparatively low dosage used (0.5 mg oestriol vaginal pessary twice weekly) [56].

Immunomodulation

Uro-Vaxom® is an oral immune stimulant containing cell wall fragments of 18 UPEC strains. A meta-analysis evaluating five RCTs concludes that treatment reduces recurrence rates up to 65% within 6–12 months after treatment in comparison to placebo [57].

Immune stimulation by parental injection is also available as a vaccination preparation called StroVac®, approved for long-term prophylactic treatment of rUTIs. It contains 10^9 inactivated pathogens from five species (*E. coli*, *Morganella morganii*, *P. mirabilis*, *K. pneumonia*, *Enterococcus faecalis*). In a recently published trial, 173 patients were offered either vaccination with StroVac® or therapy with 3 months nitrofurantoin 100 mg once daily for 3 months at patient's choice. A total of 124 patients chose StroVac® and 49 chose nitrofurantoin, associated with response rates of 86.8% vs 91.8%, respectively ($P = 0.22$). Side-effects were documented in 2.3% vs 18.4% (mostly diarrhoea) [58].

Prevention of UTI Using Antibiotic Prophylaxis

As discussed in the previously, antibiotic prophylaxis should be reserved to women who fail to respond to antibiotic-sparing strategies. Furthermore, they should have a clearly established diagnosis of rUTI and present with infection episodes at a rate that justifies such extensive antibiotic exposure. Before prescription of any antibiotic prophylaxis, patients need to be informed on the potential side-effects, including specific effects associated with the antibiotic to be used, selection of multidrug-resistant pathogens and disturbance of the gut microbiota, which may induce a broad range of other health problems, such as recurrent *Clostridioides difficile* infections (CDIs), as well as vulvovaginal and oral candidiasis.

In general, there are two types of antibiotic prophylaxis, continuous prophylaxis and postcoital prophylaxis. In women whose rUTI episodes are regularly triggered by sexual intercourse, postcoital prophylaxis may be considered. In all other cases, continuous prophylaxis should be preferred. When choosing any antibiotic prophylaxis, the susceptibility patterns of previously identified pathogens should be taken into account. The ideal duration of prophylaxis remains unclear. While there seems to be no lasting effect of prophylaxis on the frequency of rUTI, once the prophylaxis is stopped, lifelong prophylaxis carries obvious risks of increased side-effects. Therefore, to assess individual long-term response, we would initially perform prophylaxis for 3–6 months and decide on further strategy on an individual basis, if rUTI persists after stopping the antibiotic.

For postcoital prophylaxis, a single dose of antibiotic (Table 2 [21,50]) is self-administered. There is only one published placebo-controlled trial in which trimethoprim-sulfamethoxazole (40/200 mg) was randomised against placebo, resulting in 0.3 vs 3.6 episodes/patient-year, respectively [59]. However, several uncontrolled trials support the use of other antibiotics in this indication [60-62].

For continuous prophylaxis, potential options, and dosages adequate for prophylaxis are listed in Table 2. There is a solid basis for evidence to support the preventive efficacy of this approach [63]. Regimens include nitrofurantoin once daily, fosfomycin trometamol every 10 days, trimethoprim once daily. Other options, such as cephalosporins should be reserved to cases with no other treatment options, or during pregnancy, where cephalexin or cefaclor once daily could be used [21]. In a meta-analysis of 10 trials, the relative risk in patients using prophylaxis was 0.15 (95% CI 0.08–0.28). However, after termination of prophylaxis the advantage in the prophylaxis arm did not prevail [63]. Continuous prophylaxis is also considered an option for patients with urological factors predisposing to rUTI but should be avoided in patients with urinary catheters. Long-term catheters may serve as a bacterial reservoir in which resistance development is likely. Intravesical instillation of aminoglycosides has been investigated in some pilot studies, especially in rUTI caused by multidrug resistant bacteria, and has shown to reduce the number of UTI episodes and the degree of antimicrobial resistance [64].

Experimental Strategies

Besides the traditional treatment options and prophylactic therapies, new alternatives are emerging and show promising effects. In the following, two of these innovative alternatives will be introduced.

Microbiota-based Treatment

Probiotics

There are only few trials assessing the clinical efficacy of oral probiotics in preventing episodes of rUTI. The proposed mechanisms of action include blockage of epithelial attachment sites, generation of microbiocidal H_2O_2 and induction of anti-inflammatory cytokine synthesis. Out of four published trials, only one demonstrated a significant reduction of 73% in episodes of rUTI compared with the previous year (P = 0.001) [65]. Another approach is to

Table 2 Recommended antibiotic long-term prevention and post-coital measures for rUTI [21,50].

Recommendation	Antibiotic substance, dosage, mg	Regimen	Therapy duration
Ongoing long-term prevention	Cotrimoxazole, 40/200	Once daily 3 times a week	Long-term
	Trimethoprim 100	Once daily	
	Nitrofurantoin 50/100	Once daily	
	Cefaclor 250/125	Once daily	
	Fosfomycin-trometamol 3000	Every 10 days	
Postcoital one-time preventive measure	Cotrimoxazole, 40/80/200/400	Once	
	Nitrofurantoin 50/100		
	Cefalexin 125/250		

administer *Lactobacillus* spp. locally by use of vaginal capsules. In a placebo-controlled trial including 100 premenopausal women with rUTI, *Lactobacillus crispatus* was well tolerated, vaginal colonisation could be documented, and rUTI occurred in seven of 48 (15%) women in the treatment and 13/48 (27%) of women in the placebo group (risk ratio 0.5, 95% CI, 0.2–1.2) within 10 weeks of treatment [66].

Faecal Microbiota Transfer

The human gut is home to >395 bacterial phylotypes and is the focus of microbiome-research. Its composition and diversity is essential for the regulation of the host immune system, intestinal haemostasis, and resilience against pathogens [67,68]. Disruption of the physiological microbiota composition, also called dysbiosis, is associated with a broad range of diseases, including CDIs [69]. Similarly to UTIs, CDIs can present as spontaneously recurrent infections (rCDI). In this specific indication, faecal microbiota transfers (FMT) during which microorganism and metabolites of a healthy donor are transferred to patients using oral capsules, rectal enemas or endoscopically have shown to effectively interrupt the recurrent patterns with response rates of up to 80% after a single administration [68,70].

Initial reports on the impact of FMT were generated from a registry for patients receiving FMT for the indication of rCDI. A considerable proportion of these patients also presented with rUTI in addition to rCDI prior to FMT. In eight of these patients receiving a FMT, the rate of rUTI episodes was reduced from a median of 4 to 1 (range 0–4) in following the year after FMT. In a control group of eight patients with rUTI not receiving FMT, the median remained unchanged [71].

In addition to reduced frequencies, the pathogens causing the remaining UTIs in the FMT group displayed improved antibiotic susceptibilities. Many case reports have followed this observation and therefore support the hypothesis that FMT might be a promising treatment approach for rUTIs [72-75]. The underlying mechanism of action have not been elucidated but it is possible that uropathogens colonising the faecal reservoir are eradicated through the transfer of faecal microbiota, such that the source of re-infection can be eliminated.

Bacteriophages

Bacteriophages or phages are viruses that infect and replicate within bacteria. Phages have been used for the treatment of bacterial infections since the beginning of the last century; however, their use has been limited mostly to specific centres in Russia, Georgia, Poland, Belgium, and Switzerland. Phages can be administered locally or orally as phage cocktails or monotherapy and can be combined with antibiotic treatment. With the global emergence of antibiotic resistance, the clinical and scientific interest in phage treatments is experiencing a revival. Numerous case series and reports communicate highly favourable responses in individual treatment situations, and in the context of the four published RCTs assessing the safety and clinical efficacy of phage treatment, it could be shown that there seem to be very few to no treatment-related side-effects to be considered [76,77]. To date, the most promising trial assessed the efficacy of phages for the treatment of chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*. Overall, 24 patients were randomised to receive phage treatment or placebo. There was significant improvement in clinical indicators, such as inflammation, ulceration, and discharge. Moreover, patients in the treatment group showed significantly lower counts of the causative pathogen. In this trial, no adverse events related to the treatment were reported. Unfortunately, other trials, in which burn infections, infectious diarrhoea and UTIs were treated, did not succeed in demonstrating superiority of the phage treatment arm [78-80]. However, for all trials, different issues that would explain the lack of a convincing treatment response could be identified, e.g. instability and/or lack of personalisation of the phage cocktail and low concentration of phages in the cocktail. For our present review, the trial assessing the use of phages in the treatment of UTI merits further discussion. Using the commercially available phage cocktail *Pyophage* (R-022600) from Georgia, Leitner *et al.* [80] assessed the treatment of UTI in a placebo-controlled randomised trial. Overall, 113 patients identified with an UTI prior to a prostate resection were enrolled, if the identified pathogen was susceptible to *Pyophage,* which covers *Enterococcus* spp., *E. coli*, *P. mirabilis*, *P. aeruginosa*, *Staphylococcus* species and *Streptococcus* spp. In addition, Streptococcus Typ D phages were added to the cocktail to broaden its antibiotic coverage. Patients were randomised to receive intravesical treatment with the phage cocktail, placebo, or a course of antibiotics over 7 days. Overall, 28 patients received the phage cocktail at least once, but there was no difference in the response to treatment in the placebo arm. The authors hypothesised that phage titres in the cocktail were not high enough and further diluted through the intravesical application. Further trials need to be conducted to objectify the potential of phages in treating bacterial infections in general and UTI in particular.

Conclusion

Even in industrialised societies, rUTIs continue to impact the lives of a significant number of otherwise healthy women, often resulting in a reduced quality of life and repeated antibiotic exposure. Despite the high prevalence of rUTIs, the underlying pathophysiology has not been fully elucidated. Even though a number of risk factors have been identified, it is difficult to predict which patient will enter the vicious cycle of rUTI after an initial acute episode and which will not.

Besides antibiotic treatment of each acute episode, different non-antibiotic prophylactic strategies with a mostly limited evidence base can be tried before antibiotic prophylaxis may eventually become necessary. As the effects of continuous antibiotic prophylaxis persist once it is stopped, there is no long-term solution for affected patients that would not involve intense antibiotic exposure and the associated side-effects.

Novel treatment approaches involving microbiota-based treatment approaches and bacteriophages may represent a solution to this impasse but require further investments in drug development and the conduct of clinical trials.

Disclosure of Interests

Florian Waghenlehner: grants awarded by Bionorica and Klosterfrau; consulting, lecture and travel fees paid by Bionorica, Klosterfrau and GSK, leadership or fiduciary role on Guideline Group Urological Infections European Association of Urology (EAU), German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) S3 Guideline Group. Maria Vehreschild: grants awarded by 3M, Astellas Pharma, BionTech, Da Volterra, Evonik, Gilead Sciences, Gycom, Immunic, Maat Pharma, Merck/MSD, Organobalance, Seres Therapeutics, Takeda Pharmaceutical; consulting fees paid by Alb Fils Kliniken GmBH, Arderpharm, Astellas Pharma, Basilea, Biomérieux, Da Volterra, Farmak International Holding GmBH, Ferring, Gilead Sciences, Socra Tech R&D GmBH. No further disclosures.

Acknowledgment

Open access funding enabled and organized by ProjektDEAL.

References

1 **Flores-Mireles AL**, **Walker JN**, **Caparon M**, **Hultgren SJ**. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; 13: 269–84

2 **Tandogdu Z**, **Wagenlehner FME**. Global epidemiology of urinary tract infections. *Curr Opin Infect Dis* 2016; 29: 73–9

3 **Renard J**, **Ballarini S**, **Mascarenhas T et al**. Recurrent lower urinary tract infections have a detrimental effect on patient quality of life: a prospective, observational study. *Infect Dis Ther* 2015; 4: 125–35

4 **Wagenlehner F**, **Wullt B**, **Ballarini S**, **Zingg D**, **Naber KG**. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). *Expert Rev Pharmacoeconomics Outcomes Res* 2018; 18: 107–17

5 **BARMER**. BARMER GEK Arzneimittelreport, 2015. Available at: https://www.barmer.de/presse/infothek/studien-und-reports/arzneimittelreporte/report-2015-38480. Accessed November 2021

6 **Ejrnæs K**. Bacterial characteristics of importance for recurrent urinary tract infections caused by *Escherichia coli*. *Dan Med Bull* 2011; 58: B4187

7 **Ikäheimo R**, **Siitonen A**, **Heiskanen T et al**. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. *Clin Infect Dis* 1996; 22: 91–9

8 **Medina M**, **Castillo-Pino E**. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol* 2019; 11: 175628721983217

9 **Magistro G**, **Marcon J**, **Schubert S**, **Gratzke C**, **Stief CG**. Pathogenese der Harnwegsinfektion Ein update. *Der Urol Ausg A* 2017; 56: 720–7

10 **Delcaru C**, **Alexandru I**, **Podgoreanu P et al**. Microbial biofilms in urinary tract infections and prostatitis: etiology, pathogenicity, and combating strategies. *Pathogens* 2016; 5: 65

11 **Hooton TM**, **Scholes D**, **Hughes JP et al**. A prospective study of risk factors for symptomatic urinary tract infection in young women. *N Engl J Med* 1996; 335: 468–74

12 **Scholes D**, **Hawn TR**, **Roberts PL et al**. Family history and risk of recurrent cystitis and pyelonephritis in women. *J Urol* 2010; 184: 564–9

13 **Stapleton A**, **Nudelman E**, **Clausen H**, **Hakomori S**, **Stamm WE**. Binding of uropathogenic *Escherichia coli* R45 to glycolipids extracted from vaginal epithelial cells is dependent on histo-blood group secretor status. *J Clin Invest* 1992; 90: 965–72

14 **Hooton TM**, **Stapleton AE**, **Roberts PL et al**. Perineal anatomy and urine-voiding characteristics of young women with and without recurrent urinary tract infections. *Clin Infect Dis* 1999; 29: 1600–1

15 **Ejrnaes K**, **Sandvang D**, **Lundgren B et al**. Pulsed-field gel electrophoresis typing of *Escherichia coli* strains from samples collected before and after pivmecillinam or placebo treatment of uncomplicated community-acquired urinary tract infection in women. *J Clin Microbiol* 2006; 44: 1776–81

16 **Nielsen KL**, **Dynesen P**, **Larsen P**, **Frimodt-Møller N**. Faecal *Escherichia coli* from patients with *E. coli* urinary tract infection and healthy controls who have never had a urinary tract infection. *J Med Microbiol* 2014; 63: 582–9

17 **Wolfe AJ**, **Toh E**, **Shibata N et al**. Evidence of uncultivated bacteria in the adult female bladder. *J Clin Microbiol* 2012; 50: 1376–83

18 **Hilt EE**, **McKinley K**, **Pearce MM et al**. Urine is not sterile: use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. *J Clin Microbiol* 2014; 52: 871–6

19 **Stapleton AE**. The vaginal microbiota and urinary tract infection. *Microbiol Spectr* 2016; 4: 1–6. https://doi.org/10.1128/microbiolspec.UTI-0025-2016

20 **van Haarst EP**, **van Andel G**, **Heldeweg EA**, **Schlatmann TJ**, **van der Horst HJ**. Evaluation of the diagnostic workup in young women referred for recurrent lower urinary tract infections. *Urology* 2001; 57: 1068–72

21 **Bonkat G**, **Bartoletti R**, **Bruyère F et al**. EAU guidelines on urological infections. European Association of Urology, 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-infections-2021.pdf. Accessed November 2021

22 **Chang SJ**, **Tsai LP**, **Hsu CK**, **Yang SS**. Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. *Pediatr Nephrol* 2015; 30: 1131–7

23 **Cai T**, **Mazzoli S**, **Migno S et al**. Development and validation of a nomogram predicting recurrence risk in women with symptomatic urinary tract infection. *Int J Urol* 2014; 21: 929–34

24 **McDonald M**, **Kameh D**, **Johnson ME**, **Johansen TEB**, **Albala D**, **Mouraviev V**. A head-to-head comparative phase II study of standard urine culture and sensitivity versus DNA next-generation sequencing testing for urinary tract infections. *Rev Urol* 2017; 19: 213–20

25 **Anger J**, **Lee U**, **Ackerman L et al**. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol* 2019; 202: 282–9

26 **Lee SJ**, **Choe HS**, **Na YG et al**. 2017 Guidelines of the Korean association of urogenital tract infection and inflammation: recurrent urinary tract infection. *Urogenit Tract Infect* 2017; 12: 7

27 **Little P**, **Moore MV**, **Turner S et al**. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. *BMJ* 2010; 340: c199

28 **Gágyor 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; 351: h6544

29 **Wagenlehner FM**, **Abramov-Sommariva D**, **Höller 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: 327–36

30 **Gágyor I**, **Hummers E**, **Schmiemann G et al**. Herbal treatment with uva ursi extract versus fosfomycin in women with uncomplicated urinary tract infection in primary care: a randomized controlled trial. *Clin Microbiol Infect* 2021; 27: 1441–7

31 **Höller 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; 10: 685

32 **Drekonja DM**, **Trautner B**, **Amundson C**, **Kuskowski M**, **Johnson JR**. Effect of 7 vs 14 days of antibiotic therapy on resolution of symptoms among afebrile men with urinary tract infection: a randomized clinical trial. *JAMA* 2021; 326: 324–31

33 **Wong ES**, **McKevitt M**, **Running K**, **Counts GW**, **Turck M**, **Stamm WE**. Management of recurrent urinary tract infections with patient-administered single-dose therapy. *Ann Intern Med* 1985; 102: 302–7

34 **Gupta K**, **Hooton TM**, **Roberts PL**, **Stamm WE**. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. *Ann Intern Med* 2001; 135: 9–16

35 **Vahlensieck W**, **Bauer HW**, **Piechota H**, **Ludwig M**, **Wagenlehner F**. Rezidivierende Harnwegsinfektionen; Wie vermeiden und behandeln? *Dtsch Arztebl Int* 2015(Perspektiven der Urologie); 112: 16–9

36 **Hooton TM**, **Vecchio M**, **Iroz A et al**. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. *JAMA Intern Med* 2018; 178: 1509–15

37 **Kaur R**, **Kaur R**. Symptoms, risk factors, diagnosis and treatment of urinary tract infections. *Postgrad Med J* 2020 (Online ahead of print). https://doi.org/10.1136/postgradmedj-2020-139090

38 **Fihn SD**, **Boyko EJ**, **Normand EH et al**. Association between use of spermicide-coated condoms and *Escherichia coli* urinary tract infection in young women. *Am J Epidemiol* 1996; 144: 512–20

39 **Baerheim A**, **Laerum E**. Symptomatic lower urinary tract infection induced by cooling of the feet. A controlled experimental trial. *Scand J Prim Health Care* 1992; 10: 157–60

40 **Schmidt DR**, **Sobota AE**. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988; 55: 173–81

41 **Stapleton AE**, **Dziura J**, **Hooton TM et al**. Recurrent urinary tract infection and urinary *Escherichia coli* in women ingesting cranberry juice daily: a randomized controlled trial. *Mayo Clin Proc* 2012; 87: 143–50

42 **Beerepoot MAJ**, **ter Riet G**, **Nys S et al**. Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. *Arch Intern Med* 2011; 171: 1270–8

43 **Avorn J**, **Monane M**, **Gurwitz JH**, **Glynn RJ**, **Choodnovskiy I**, **Lipsitz LA**. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994; 271: 751–4

44 **Wang CH**, **Fang CC**, **Chen NC et al**. Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; 172: 988–96

45 **Luís Â**, **Domingues F**, **Pereira L**. Can Cranberries contribute to reduce the incidence of urinary tract infections? A systematic review with meta-analysis and trial sequential analysis of clinical trials. *J Urol* 2017; 198: 614–21

46 **Lenger SM**, **Bradley MS**, **Thomas DA**, **Bertolet MH**, **Lowder JL**, **Sutcliffe S**. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2020; 223: 265.e1–13

47 **Kranjčec B**, **Papeš D**, **Altarac S**. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol* 2014; 32: 79–84

48 **Damiano R**, **Quarto G**, **Bava I et al**. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. *Eur Urol* 2011; 59: 645–51

49 **Constantinides C**, **Manousakas T**, **Nikolopoulos P**, **Stanitsas A**, **Haritopoulos K**, **Giannopoulos A**. Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. *BJU Int* 2004; 93: 1262–6

50 Interdisziplinäre S3 Leitlinie: Epidemiologie, Diagnostik, Therapie, Prevention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten. *AWMF-Register-Nr. 043/044* 2017(Version 1.1-2)

51 **Botros C**, **Lozo S**, **Iyer S et al**. Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial. *Int Urogynecol J* 2021 (Online ahead of print). https://doi.org/10.1007/s00192-021-04849-0

52 **Larsson B**, **Jonasson A**, **Fianu S**. Prophylactic effect of UVA-E in women with recurrent cystitis: a preliminary report. *Curr Ther Res* 1993; 53: 441–3

53 **Albrecht U**, **Goos KH**, **Schneider B**. A randomised, double-blind, placebo-controlled trial of a herbal medicinal product containing *Tropaeoli majoris* herba (Nasturtium) and *Armoraciae rusticanae* radix (Horseradish) for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections. *Curr Med Res Opin* 2007; 23: 2415–22

54 **Raul R**, **Stamm WE**. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993; 329: 753–6

55 **Eriksen BC**. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *Am J Obstet Gynecol* 1999; 180: 1072–9

56 **Raz R**, **Colodner R**, **Rohana Y et al**. Effectiveness of estriol-containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. *Clin Infect Dis* 2003; 36: 1362–8

57 **Bauer HW**, **Rahlfs VW**, **Lauener PA**, **Bleßmann GS**. Prevention of recurrent urinary tract infections with immuno-active *E. coli* fractions: a meta-analysis of five placebo-controlled double-blind studies. *Int J Antimicrob Agents* 2002; 19: 451–6

58 **Nestler S**, **Grüne B**, **Schilchegger L**, **Suna A**, **Perez A**, **Neisius A**. Efficacy of vaccination with StroVac for recurrent urinary tract infections in women: a comparative single-centre study. *Int Urol Nephrol* 2021; 53: 2267–72

59 **Stapleton A**. Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. *JAMA* 1990; 264: 703

60 **Chew L**, **Fihn S**. Recurrent cystitis in nonpregnant women. *West J Med* 1999; 170: 274–7

61 **Pfau A**, **Sacks T**, **Engelstein D**. Recurrent urinary tract infections in premenopausal women: prophylaxis based on an understanding of the pathogenesis. *J Urol* 1983; 129: 1153–7

62 **Pfau A**, **Sacks TG**. Effective postcoital quinolone prophylaxis of recurrent urinary tract infections in women. *J Urol* 1994; 152: 136–8

63 **Albert X**, **Huertas I**, **Pereiró II**, **Sanfélix J**, **Gosalbes V**, **Perrota C**. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev* 2004; 3: CD001209

64 **Stalenhoef JE**, **van Nieuwkoop C**, **Menken PH**, **Bernards ST**, **Elzevier HW**, **van Dissel JT**. Intravesical gentamicin treatment for recurrent urinary tract infections caused by multidrug resistant bacteria. *J Urol* 2019; 201: 549–55

65 **Barrons R**, **Tassone D**. Use of Lactobacillus probiotics for bacterial genitourinary infections in women: a review. *Clin Ther* 2008; 30: 453–68

66 **Stapleton AE**, **Au-Yeung M**, **Hooton TM et al**. Randomized, placebo-controlled phase 2 trial of a *Lactobacillus crispatus* probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clin Infect Dis* 2011; 52: 1212–7

67 **Macpherson AJ**, **Harris NL**. Interactions between commensal intestinal bacteria and the immune system. *Nat Rev Immunol* 2004; 4: 478–85

68 **van Nood E**, **Vrieze A**, **Nieuwdorp M et al**. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368: 407–15

69 **Magill SS**, **Edwards JR**, **Bamberg W et al**. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014; 370: 1198–208

70 **Borody TJ**, **Campbell J**. Fecal microbiota transplantation: techniques, applications, and issues. *Clin North Am Gastroenterol* 2012; 41: 781–803

71 **Tariq R**, **Pardi DS**, **Tosh PK**, **Walker RC**, **Razonable RR**, **Khanna S**. Fecal microbiota transplantation for recurrent clostridium difficile infection reduces recurrent urinary tract infection frequency. *Clin Infect Dis* 2017; 65: 1745–7

72 **Wang T**, **Kraft CS**, **Woodworth MH**, **Dhere T**, **Eaton ME**. Fecal microbiota transplant for refractory clostridium difficile infection interrupts 25-year history of recurrent urinary tract infections. *Open Forum Infect Dis* 2018; 5: ofy016

73 **Biehl LM**, **Cruz Aguilar R**, **Farowski F et al**. Fecal microbiota transplantation in a kidney transplant recipient with recurrent urinary tract infection. *Infection* 2018; 46: 871–4

74 **Bier N**, **Blake H**, **Jiang ZD**, **DuPont HL**, **Arias CA**, **Miller WR**. Successful gut decoloniozation of extended-spectrum ß-lactamase producing *Klebsiella pneumoniae* using oral lyophilized fecal microbiota transplant (FMT) in a woman with recurrent urinary tract infections. *Open Forum Infect Dis* 2020; 7: 830–31

75 **Keen EC**, **Tasoff P**, **Hink T et al**. Microbiome restoration by RBX2660 does not preclude recurrence of multidrug-resistant urinary tract infection following subsequent antibiotic exposure: a case report. *Open Forum Infect Dis* 2020; 7: ofaa042

76 **Clarke A**, **De Soir S**, **Jones J**. The safety and efficacy of phage therapy for bone and joint infections: a systematic review. *Antibiotics* 2020; 9: 795

77 **Gibb BP**, **Hadjiargyrou M**. Bacteriophage therapy for bone and joint infections. *Bone Joint J* 2021; 103-B: 234–44

78 **Sarker SA**, **Sultana S**, **Reuteler G et al**. Oral phage therapy of acute bacterial diarrhea with two coliphage preparations: a randomized trial in children from Bangladesh. *EBioMedicine* 2016; 4: 124–37

79 **Jault P**, **Leclerc T**, **Jennes S et al**. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis* 2019; 19: 35–45

80 **Leitner L**, **Ujmajuridze A**, **Chanishvili N et al**. Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. *Lancet Infect Dis* 2021; 21: 427–36

Correspondence: Florian Wagenlehner, Clinic of Urology, Pediatric Urology and Andrology, Justus Liebig University Giessen, Rudolf-Buchheim-Str. 7, 35392 Giessen, Germany.

e-mail: florian.wagenlehner@chiru.med.uni-giessen.de

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, faecal microbiota transfer; GAG, glycosaminoglycan; NSAR, non-steroidal anti-rheumatics; RCT, randomised controlled trial; rUTI, recurrent UTI; UPEC, uropathogenic *Escherichia coli*.