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The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention

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Keywords
Urinary tract infection · Cystitis · Pyelonephritis · Therapy · Systematic review · Clinical guideline

Abstract
Background: We aimed to update the 2010 evidence- and consensus-based national clinical guideline on the diagnosis and management of uncomplicated urinary tract infections (UTIs) in adult patients. Results are published in 2 parts. Part 1 covers methods, the definition of patient groups, and diagnostics. This second publication focuses on treatment of acute episodes of cystitis and pyelonephritis as well as on prophylaxis of recurrent UTIs. ***Materials and Methods:*** An interdisciplinary group consisting of 17 representatives of 12 medical societies and a patient representative was formed. Systematic literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library to identify literature published in 2010–2015. ***Results:*** For the treatment of acute uncomplicated cystitis (AUC), fosfomycin-trometamol, nitrofurantoin, nitroxoline, pivmecillinam, and trimethoprim (depending on the local rate of resistance) are all equally recommended. Cotrimoxazole, fluoroquinolones, and cephalosporins are not recommended as antibiotics of first choice, for concern of an unfavorable impact on the microbiome. Mild to moderate uncomplicated pyelonephritis should be treated with oral cefpodoxime,

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ceftibuten, ciprofloxacin, or levofloxacin. For AUC with mild to moderate symptoms, instead of antibiotics symptomatic treatment alone may be considered depending on patient preference after discussing adverse events and outcomes. Primarily non-antibiotic options are recommended for prophylaxis of recurrent urinary tract infection. ***Conclusion:*** In accordance with the global antibiotic stewardship initiative and considering new insights in scientific research, we updated our German clinical UTI guideline to promote a responsible antibiotic use and to give clear hands-on recommendations for the diagnosis and management of UTIs in adults in Germany for healthcare providers and patients.

Background

Uncomplicated, bacterial, community-acquired urinary tract infections (UTIs), including cystitis and pyelonephritis, are among the most common infections in the outpatient setting. Antibiotic resistance is a growing global problem that leads to significant challenges and costs in the health care system [1–4]. We updated the German clinical UTI guideline to promote a responsible antibiotic use in the management of UTIs in adults in Germany.

The German AWMF S3 guideline is free for download available in a short and long version on the website of the AWMF (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften) (http://www.awmf.org/leitlinien/detail/ll/043–044.html) [6]. The category S3 refers to the German guideline classification form, where S3 represents the highest methodological standard and involves both evidence- and consensus-based concept to achieve guideline recommendations from an interdisciplinary panel group [5].

We present the main content of the updated guideline in 2 parts. Part I focuses on the recommendations regarding the definition of patient groups and the diagnostics of uncomplicated bacterial UTI acquired in the outpatient setting in adult patients and was already published [6]. This publication of part II covers the treatment of acute episodes of cystitis and pyelonephritis as well as the prevention of recurrent UTIs (rUTI) in otherwise healthy women in the premenopause (standard group). Recommendations concerning other patient's groups are found in the long version of the S3 guideline (see above). There is also a German publication available that covers the latest changes of this guideline update [7].

Objective

We aimed to update the 2010 evidence- and consensus-based national guideline on the diagnostics and management of uncomplicated UTIs in adult patients. Specific objectives were (a) to promote a rational use of antimicrobial substances, (b) to avoid an inappropriate use of antibiotic therapies (i.e., use without indication), and (c) to avoid the development of antibiotic resistance.

Methods

This AWMF S3 clinical guideline is based on an interdisciplinary consensus group consisting of 17 representatives of 12 medical societies and a member of a patient organization (Table 1). Details on the methodological process are described elsewhere [6].

Recommendations are based on a systematic literature search that was conducted between 2010 and 2015. The Oxford criteria were used for the level of evidence (I-V) ratings [8]. Recommendations were graded as follows:

A: strong recommendation: should/should not
B: weak recommendation: ought to/ought not to
C: recommendation inconclusive: may be considered.

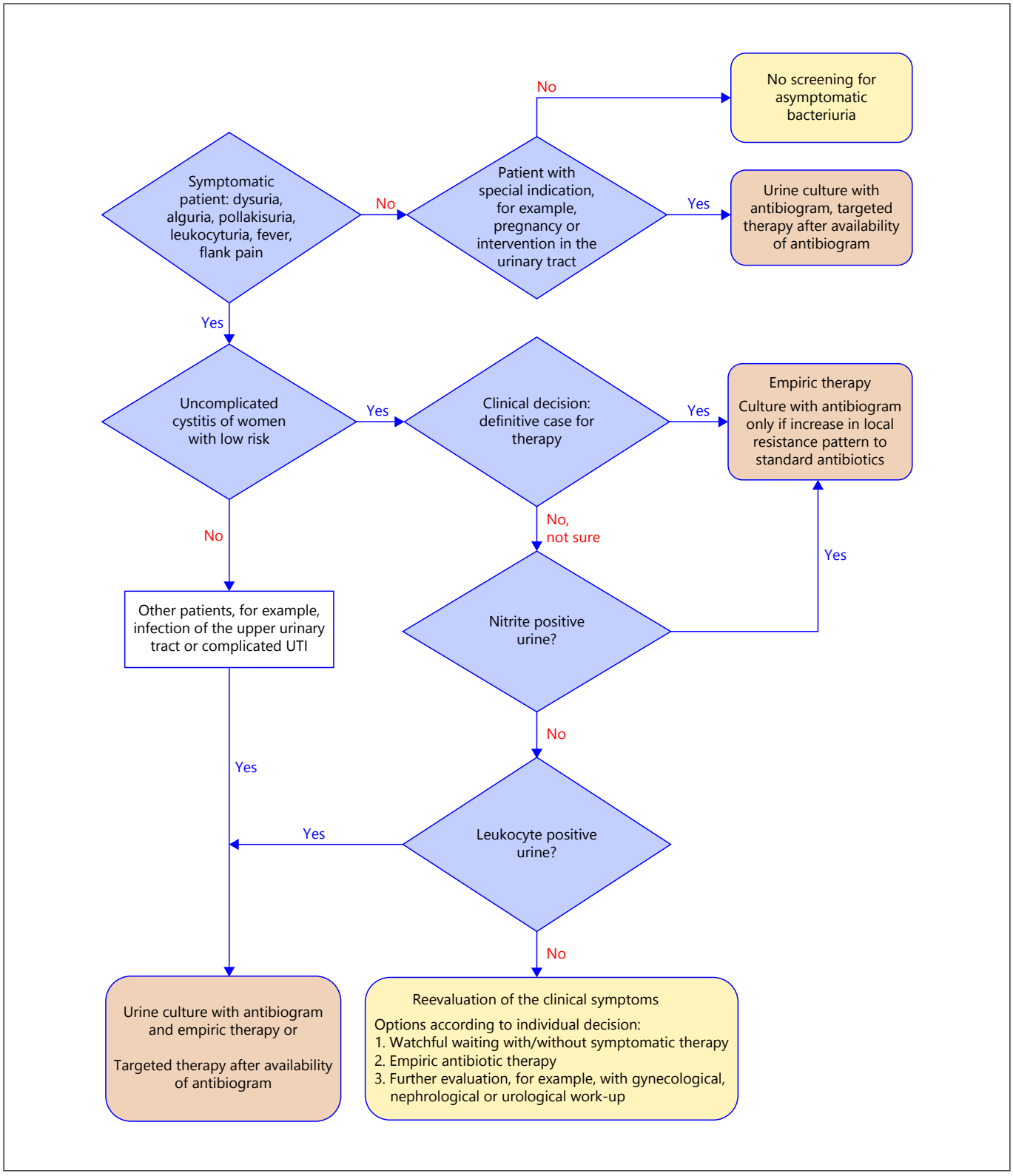
Results

Figure 1 presents a decision tree on diagnosis and treatment in symptomatic patients. The following criteria should be taken into account when deciding which antibiotic to use (Ia-A):

- Patient's individual risk
- Spectrum of pathogens and antibiotic sensitivity
- Efficacy of the antimicrobial substance
- Adverse drug reactions
- Effects on the microbiome in the individual patient (collateral damage) and/or the general population (epidemiological effects).

Acute Uncomplicated Cystitis: Standard Group (Otherwise Healthy Women in the Premenopause)

The spontaneous recovery rate in acute uncomplicated cystitis (AUC) is high (at 1 week: clinically 28%, clinically and microbiologically 37%). The central goal of treatment is swift relief of the clinical symptoms, that is, within a matter of days [9]. The small number of placebo-controlled studies has shown that the symptoms resolve more rapidly with antibiotic treatment than with placebo [10]. In a recent study, Gágyor et al. [11] compared the effect of primarily symptomatic ibuprofen treatment with that of immediate administration of an antibiotic. Around two-



Color version available online

Fig. 1. Decision tree – diagnosis and treatment in symptomatic patients (clinical-microbiological diagnostic pathway). On the initial manifestation of acute UTI, or if the patient is unknown to the physician, the medical history should be documented and a symptom-oriented medical examination carried out.

Table 1. Participating medical societies and working groups

Medical society or working group	Participants in the update 2017
German Society of Urology (DGU) – lead organization	Dr. Jennifer Kranz Prof. Dr. Kurt Naber Dr. Stefanie Schmidt Dr. Laila Schneidewind Priv. Doz. Dr. Winfried Vahlensieck Prof. Dr. Florian M. Wagenlehner
German College of General Practitioners and Family Physicians (DEGAM)	Prof. Dr. E. Hummers Priv.-Doz. Dr. Guido Schmiemann
German Society of Gynecology and Obstetrics (DGGG)	Prof. Dr. U. Hoyme Dr. Mirjam Kunze
German Society for Hygiene and Microbiology (DGHM)	Dr. E. Kniehl
German Society of Infectious Diseases (DGI)	Dr. Sina Helbig Dr. Falitsa Mandraka
German Society of Nephrology (DGfN)	Prof. Dr. R. Fünfstück Prof. Dr. U. Sester
Paul Ehrlich Society for Chemotherapy (PEG)	Prof. Dr. R. Fünfstück Dr. E. Kniehl Prof. Dr. Kurt Naber Prof. Dr. Florian M. Wagenlehner
German Society for Clinical Chemistry and Laboratory Medicine (DGKL)	Prof. Dr. W. Hofmann
German Association of Pharmacists (AKDA)	Dr. Cordular Lebert
Patient representative, Interstitielle Cystitis Association Deutschland (ICA-D)	B. Mündner-Hensen

DGU, Deutsche Gesellschaft für Urologie; DEGAM, Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin; DGHM, Deutsche Gesellschaft für Hygiene und Mikrobiologie; DGI, Deutsche Gesellschaft für Infektiologie; DGfN, Deutsche Gesellschaft für Nephrologie; PEG, Paul-Ehrlich-Gesellschaft für Chemotherapie; DGKL, Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin.

thirds of patients with purely symptomatic treatment needed no further antibiotic. Meanwhile, in another recent study, a symptomatic treatment with non-steroidal anti-inflammatory drugs was compared with immediate antibiotic therapy. Rate of antibiotic prescriptions could also be reduced significantly [12]. In light of these findings, non-antibiotic, symptomatic treatment can be considered in cases of AUC with mild or moderate symptoms (IA-B). Due consideration should be paid to the patients' preferences when deciding what course of treatment to follow. This is especially true for primarily non-antibiotic treatment, which may be associated with a greater burden of symptoms (symptom-free after 7 days: ibuprofen 163 of 232 patients versus fosfomycin 186 of 227 patients, 95% CI [–19.4 to –4.0]) [11]. Patients' preferences have to be taken into account and the decision should be made after discussing adverse events and outcomes.

Asymptomatic Bacteriuria

In general, asymptomatic bacteriuria (ASB) does neither need screening nor treatment. The presence of ASB, however, increases the risk of infection for patients undergoing urinary tract interventions in which mucosal trauma can be anticipated. Therefore, in such cases, ASB should be actively sought, and if present, it should be treated (Ia-A) [13]. The evidence from randomized studies in this respect exists primarily for transurethral resection of the prostate. However, high level evidence is lacking regarding low-risk interventions, for example, urethrocystoscopy.

Kazemier et al. [14] showed that in women low-risk pregnancy and ASB the risk of symptomatic cystitis increased from 7.9 to 20.2% if they were treated with placebo or not at all (for pyelonephritis from 0.6 to 2.4%). However, ASB did not increase the risk of premature birth for non-treated patients [14].

Table 2. Recommended empirical short-term antibiotic treatment of uncomplicated cystitis in women in the premenopause (standard group; listing in alphabetic order)

Substance	Daily dose	Duration, days	Eradication rate in sensitive pathogens	Sensitivity	Collateral damage	Safety/ADR
The following antibiotics should be used preferentially in the treatment of uncomplicated cystitis						
Fosfomycin-trometamol	3,000 mg 1 × daily	1	++	+++	+++	+++
Nitrofurantoin	50 mg 4 × daily	7	+++	+++	+++	++
Nitrofurantoin RT (slow-release form)	100 mg 2 × daily	5	+++	+++	+++	++
Nitroxolin	250 mg 3 × daily	5	+++	+++	+++	+++
Pivmecillinam	400 mg 2–3 × daily	3	+++	+++	+++	+++
Trimethoprim should not be used as drug of first choice if local resistance to E. coli *is >20%*						
Trimethoprim	200 mg 2 × daily	3	+++	+(+)	++	++(+)
The following antibiotics should not be used as drugs of first choice in the treatment of uncomplicated cystitis						
Cefpodoxim-proxetil	100 mg 2 × daily	3	++	++	+	+++
Ciprofloxacin	250 mg 2 × daily	3	+++	++	+	++
Cotrimoxazol	160/800 mg 2 × daily	3	+++	+(+)	++	++
Levofloxacin	250 mg 1 × daily	3	+++	++	+	++
Norfloxacin	400 mg 2 × daily	3	+++	++	+	++
Ofloxacin	200 mg 2 × daily	3	+++	++	+	++

Symbol	Eradication, %	Sensitivity, %	Collateral damage	Safety/ADR
+++	>90	>90	Little selection of multiple drug resistant pathogens, little development of resistance to own class of antibiotics	High safety, slight ADR
++	80–90	80–90	Little selection of multiple drug resistant pathogens, development of resistance to own class of antibiotics	Severe ADR possible
+	<80	<80	Selection of multiple drug resistant pathogens, development of resistance to own class of antibiotics	n.a.

ADR, adverse drug reactions.

General Comment on Antibiotic Treatment of AUC

Among the group of antibiotics or classes of antibiotic drugs that are basically suitable for the treatment of AUC – aminopenicillins in combination with a beta-lactamase inhibitor, groups 2 and 3 cephalosporins, fluoroquinolones, fosfomycin-trometamol, nitrofurantoin, nitroxoline, pivmecillinam, trimethoprim, or cotrimoxazole – the fluoroquinolones and cephalosporins are associated with the greatest risk of microbiological collateral damage by selection of multiple drug resistant pathogens or an elevated risk of Clostridium difficile-associated colitis [15].

Since fluoroquinolones and cephalosporins have an important role in the treatment of complicated infections, the clinical consequences of increased resistance by their use in uncomplicated infections were rated as more severe than for other antibiotics recommended for the treatment of AUC (V). Therefore, fluoroquinolones and cephalosporins should not be used in the treatment of AUC unless there is no alternative (V-A; Table 2). Cotrimoxazole is also not recommended, because it is not more efficacious than trimethoprim mono, but exhibits a higher rate of adverse events. In addition, patient-relevant clinical endpoints (clinical improvement of symptoms, recurrences, ascending infections) and the individual risk (e.g., tendon rupture with the fluoroquinolones) should be taken into account.

Acute Uncomplicated Pyelonephritis: Standard Group

Patients with acute uncomplicated pyelonephritis (AUP) should receive efficacious antibiotic treatment as soon as possible, because of possible kidney damage [16], which is more likely with increasing duration, and severity of pyelonephritis. In choosing the best antibiotic to use, the eradication rates, sensitivity, collateral damage, and special characteristics regarding adverse drug reactions should be taken into account (V; Table

Table 3. Recommended empirical antibiotic treatment of uncomplicated pyelonephritis in women in the premenopause (standard group)

Substance	Daily dose	Duration, days	Eradication rate in sensitive pathogens	Sensitivity	Collateral damage	Safety/ADR
Oral treatment in mild to moderate infection						
Ciprofloxacin[1]	500–750 mg 2 × daily	7–10	+++	++	+	++
Levofloxacin	750 mg 1 × daily	5	+++	++	+	++
Cefpodoxim-proxetil	200 mg 2 × daily	10	+++	++	+	+++
Ceftibuten[2]	400 mg 1 × daily	10	+++	++	+	+++
Initial parenteral therapy in severe infection Following improvement, in the presence of pathogen sensitivity oral sequential treatment with one of the above-mentioned oral agents can be initiated. The total duration of treatment is 1–2 weeks; therefore, no duration of treatment is given for the parenteral antibiotics						
First-choice drugs						
Ciprofloxacin	400 mg (2)–3 × daily		+++	++	+	++
Levofloxacin	750 mg 1 × daily		+++	++	+	++
Ceftriaxon[1, 3]	(1)–2 g 1 × daily		+++	++	+	+++
Cefotaxim[4]	2 g 3 × daily		+++	++	+	+++
Second-choice drugs						
Amoxicillin/clavulanic acid[4, 5]	2.2 g 3 × daily		++	+	+++	+++
Amikacin	15 mg/kg 1 × daily		++	++	++	+(+)
Gentamicin	5 mg/kg 1 × daily		++	++	++	+(+)
Cefepime[1, 3]	(1)–2 g 2 × daily		+++	++	+	+++
Ceftazidime[2]	(1)–2 g 3 × daily		+++	++	+	+++
Ceftazidime/avibactam	2.5 g 3 × daily		+++	+++	++	+++
Ceftolozan/tazobactam	1.5 g 3 × daily		+++	+++	++	+++
Piperacillin/tazobactam[1, 3]	4.5 g 3 × daily		+++	+++	++	+++
Ertapenem[3, 6]	1 g 1 × daily		+++	+++	++	+++
Imipenem/cilastatin[1, 3, 6]	1 g/1 g 3 × daily		+++	+++	++	+++
Meropenem[3, 6, 7]	1 g 3 × daily		+++	+++	++	+++

[1] Low dosage investigated, high dosage recommended by experts.
[2] No longer on sale in Germany.
[3] Same protocol for acute uncomplicated pyelonephritis and complicated urinary tract infection (stratification not always possible).
[4] Not investigated as sole substance in acute uncomplicated pyelonephritis.
[5] Principally for gram-positive pathogens.
[6] Only in extended-spectrum betalactamase resistance >10%.
[7] Only high dosages investigated. Symbols as explained in Table 2.
ADR, adverse drug reactions.

3). As the prevalence is much lower than that of AUC (0.16%) [17], less heed has to be paid to collateral damage [17].

Prevention of Recurrent Urinary Tract Infection: Standard Group

Before initiation of long-term prophylactic drug treatment, a woman with rUTI should be counseled in detail on avoidance of risks (e.g., not drinking enough, overcooling, excessive intimate hygiene; Ib-A) [18, 19]. If rUTI persists despite appropriate preventive measures, long-term non-antibiotic prophylaxis ought to be preceded by oral administration of an *Escherichia coli* lysate (OM-89) for 3 months (Ia-B) [20]. Immunoprophylaxis by means of 3 parenteral injections of inactivated specified enterobacteria at 1-week intervals can be used (Ib-C) [14]. Moreover, mannose can be recommended (Ib-C) [21]; alternatively, various phytotherapeutic agents (bearberry leaves with dandelion root and horseradish root with nasturtium herb proven in studies) may be considered (Ib-C) [22, 23]. If the patient's level of suffering is high, failure of behavioral modifica-

Table 4. Long-term antibiotic prevention of recurring UTI (after [16])

Substance	Dosage	Anticipated UTI rate per patient year	Sensitivity	Collateral damage	Safety/ADR
Continuous long-term prophylaxis					
Cotrimoxazol	40/200 mg 1 × daily	0–0.2	+(+)	++	++
Cotrimoxazol	40/200 mg 3 × weekly	0.1	+(+)	++	++
Trimethoprim	100 mg 1 × daily[1]	0–1.5	+(+)	++	+++
Nitrofurantoin	50 mg 1 × daily	0–0.6	+++	+++	++
Nitrofurantoin	100 mg 1 × daily[2]	0–0.7	+++	+++	++
Cefaclor	250 mg 1 × daily[3]	0.0	No data	+	+++
Cefaclor	125 mg 1 × daily[3]	0.1	No data	+	+++
Norfloxacin	200 mg 1 × daily[3]	0.0	++	+	++
Ciprofloxacin	125 mg 1 × daily[3]	0.0	++	+	++
Fosfomycin-Trometamol	3 g every 10 days	0.14	+++	+++	+++
Postcoital single-dose prophylaxis					
Cotrimoxazol	40/200 mg	0.3	+(+)	++	++
Cotrimoxazol	80/400 mg	0.0	+(+)	++	++
Nitrofurantoin	50 mg	0.1	+++	+++	++
Nitrofurantoin	100 mg[2]	0.1	+++	+++	++
Cefalexin	250 mg[3]	0.0	No data	+	+++
Cefalexin	125 mg[3]	0.0	No data	+	+++
Norfloxacin	200 mg[3]	0.0	++	+	++
Ofloxacin	100 mg[3]	0.03	++	+	++

[1] In older studies, trimethoprim 50 mg was reported as equivalent to 100 mg.
[2] In the case of equivalent, nitrofurantoin 50 mg is the dose of choice.
[3] To avoid collateral damage and above all increasing resistance; use only if the other substances cannot be used.
ADR, adverse drug reactions; UTI, urinary tract infections.
Symbols as explained in Table 2.

tion and non-antibiotic prophylaxis ought to be followed by continual long-term antibiotic prophylaxis for 3–6 months (IV-B) [17] (Table 4). In the presence of an association with sexual intercourse, postcoital prophylaxis with a single dose ought to be used instead of long-term administration of antibiotics (Ib-B) [17, 24, 25].

Conclusion

The high frequency of uncomplicated bacterial community-acquired UTIs in adults and their treatment and prophylaxis with antibiotics exerts massive antibiotic selection pressure on the microbiome, resulting in significant influence on the selection of antibiotic-resistant bacteria in the population. Rational use of antibiotics for this indication is therefore prudent in safeguarding the efficacy of antibiotic treatment (antibiotic stewardship). The evidence and consensus-based recommendations of the updated S3 guideline therefore need to be widely implemented.

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