S-3 Guideline uncomplicated urinary tract infections.

Guidelines on the epidemiology, diagnostics, therapy and management of uncomplicated bacterial community acquired urinary tract infections in adults

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Abstract: Urinary tract infections (UTI) belong to the most frequent bacterial infections in outpatients. Increasing antibiotic resistance rates and a new appreciation of the epidemiological side effects of antibiotics (“collateral damage”) have warranted an update of the guidelines of uncomplicated UTI as an S3 clinical guideline. Methods: The guideline was developed by the Deutsche Gesellschaft für Urologie (DGU), in collaboration with the Deutsche Gesellschaft für Allgemein- und Familienmedizin (DEGAM), Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM), Deutsche Gesellschaft für Infektiologie (DGI), Deutsche Gesellschaft für Nephrologie (DGfN), Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG) and a patient representative. The systematic review of the literature on the topics of the guideline was performed for the time period 01.01.1998 to 30.04.2008 in the data-bases Cochrane Library and Medline. International guidelines of the years 1999 to 2007 were included. Results: Uncomplicated UTI comprise uncomplicated cystitis and uncomplicated pyelonephritis. The leading uropathogen is Escherichia coli. The choice of the antibiotic substance follows the five primary aspects: 1. individual patient risk and antibiotic pretreatment; 2. bacterial spectrum and antibiotic susceptibility; 3. effectivety of the antimicrobial substance demonstrated in clinical studies; 4. epidemiological effects (“collateral damage”) and 5. adverse effects. If antibiotics such as trimethoprim/sulfamethoxazole or fluoroquinolones have been given prior, the risk for pathogens to become resistant against these substances is increased. Because of in-breasing resistance rates of E. coli against trimethoprim/sulfamethoxazole also in uncomplicated UTI, trimethoprim alone or in combination with sulfamethoxazole is not regarded any more as first line agent in the empiric treatment of uncomplicated cystitis, unless the regional resistance rate is below 20%. The antibiotic resistance rates of fluoroquinolones in uncomplicated UTI are in Germany still below 10%. But there is a significant emergence of resistance compared to earlier years. Moreover fluoroquinolones and group 3 cephalosporines exhibit negative epidemiological effects resulting in selection of multi-resistant pathogens. Because these antibiotic classes are needed in therapy of life-threatening infections, such effects should be taken seri-ously. For substances like fosfomycin, nitrofurantoin or mecillinam “collateral damage” has not been documented or only to a lesser degree. Therefore for empiric therapy of frequent uncomplicated cystitis fosfomycin-trometamol, nitrofurantoin or pivmecillinam (not listed in Germany) are recommended as first-line antibiotics. For oral first-line treatment of uncomplicated pyelo-nephritis fluoroquinolones are still recommended in sufficiently high dosage, due to the resist-ance rates of E. coli still being below 10% and the superior effectivity compared to other anti-biotics. Asymptomatic bacteriuria (ASB) should only be treated in exceptional cases such as pregnant women or prior to expect-ed mucocutaneous traumatising interventions of the urinary tract. Conclusion: The S3 guideline „uncomplicated urinary tract infections“ is a comprehensive set of evidence-and consensus-based recommendations dealing with epidemiology, diagnosis, therapy and management of uncomplicated bacterial UTI of adult outpatients. A broad implementation in all disciplines taking care of patients with UTI is necessary, in order to ensure a prudent anti-biotic policy in these frequent infections and thus improve patient care.

1. BACKGROUND

The clinical S3-guideline uncomplicated urinary tract infections (UTI) aims to implement evidence based guidelines on the diagnosis and therapy of uncomplicated bacterial community acquired UTI in adults, in order to prevent unbalanced use of certain antibiotic classes and thus prevent emergence of antibiotic resistance.

Guidelines in Germany are classified according to the “Arbeitsgemeinschaft Wissenschaftlich Medizinischer Fachgesellschaften (AWMF)” into three classes (S1, S2, S3), depending on the methodology of development¹. A S3-guideline is the highest scientific level and encompasses a guideline with all elements of systematic development (logic-, decision- and outcome analysis)³.

This S3-guideline was initiated by Prof. Dr. K.G. Naber and Prof. Dr. F.M.E. Wagenlehner and was endorsed by the Deutsche Gesellschaft für Urologie (DGU). The scientific societies, work-ing groups, organisations and authors with voting power are shown in figure 1. The guideline was supported by the “Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)” (Prof. Dr. I. Kopp). International reviewers have reviewed and evaluated this version of the guideline.

The full German long-version of the consented S3-guideline can be downloaded from the web-sites of the AWMF, the DGU and other participating societies. This publication corresponds to the short-version, which is available in the German and English version.
2. METHODS

The consensus-group of this S3-guideline consisted of 11 representatives of 7 societies and one patient representative (Figure 1). Defined topics were distributed in working groups. The recommendations are based on the systematic literature research performed through the databases Cochrane Library and Medline, searching the period from 1st January 1998 through 30th April 2008. 13 international guidelines were included in the evidence process6-18. The evaluation of the scientific evidence was performed in five evidence grades (I-V) according to the Oxford Centre of Evidence Based Medicine19 (Table 1). Four recommendations were given: A - strong recommendation; B - recommendation; C - recommendation uncertain; D - no recommendation possible.11 consensus conferences were held, the consensus process was achieved by a nominal group process (NGP) lead by an external moderator of the AWMF with the representatives of the involved societies.

3. INTRODUCTION

Uncomplicated UTI are amongst the most frequent infections in the outpatient setting and are together with respiratory infections responsible for the highest amount of antibiotic prescriptions. The first evidence based recommendations on uncomplicated UTI were published by the Infectious Disease Society of America in 1999.20 Since then the resistance level of the uropathogens causing uncomplicated UTI has considerably increased and different therapeutic strategies have been evaluated. The knowledge and awareness for collateral effects of systemic antibiotic substances has increased considerably. These aspects have internationally lead to a reconsideration of recommendations and guidelines in uncomplicated UTI.21-23. This short version contains the most important fundamentals and all consented recommendations. The exact description of the methods and the detailed explanations with corresponding references are to be found only in the long version.

5. GROUPS OF PATIENTS

Patients with uncomplicated UTI should be discerned into different groups with regard to diagnostic procedure and therapy (B-V).
- otherwise healthy, non-pregnant premenopausal women (standard group)
- otherwise healthy pregnant women
- otherwise healthy postmenopausal women
- otherwise healthy young men
- otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

5.1. Otherwise healthy, non-pregnant premenopausal women
In otherwise healthy, non-pregnant women the following factors increase the risk for UTI (A).
- recent intercourse (IIb)
- use of diaphragm and spermicides (IIb)
- previous asymptomatic bacteriuria (IIb)
- UTI in the medical history (IIb)
- young age at first UTI (IIb)
- UTI in family medical history (IIb)

The incidence of cystitis and pyelonephritis is greater in women than in men in this age group (IIb).
Asymptomatic bacteriuria is often found during routine examinations in otherwise healthy non pregnant women. Asymptomatic bacteriuria does not require treatment in this group of patients apart from some exceptions (Ia).

5.2. Otherwise healthy pregnant women without risk factors
UTI and asymptomatic bacteriuria are more frequent in pregnancy (Ia).

The spectrum of pathogens and the bacterial resistance patterns are similar to non-pregnant premenopausal women (Ia).
The rate of pyelonephritis, compared to non pregnant women is increased (IIa).

There seem to be correlations between UTI and asymptomatic bacteriuria in pregnancy and pre-term delivery, reduced birth weight, increased neonatal mortality and preclampsia (IIb).

5.3. Otherwise healthy postmenopausal women
Postmenopause is characterized by a significantly decreased estrogen production, which is often associated with atrophy of the vaginal mucous membranes. A change in pH and a reduced colo-nization by lactobacilli leads to an increased vaginal colonization with enterobacteriaceae and anaerobes. Their increasing concentration predisposes to UTI, with a correlation to increasing age (IIb).

According to an American epidemiological study 6.7 episodes of UTI are expected per 100 per son years in postme-nopausal diabetic women (IIb).

There are epidemiological studies on the incidence of cystitis and pyelonephritis in postmeno-pausal women (IIb).

For female nursing home residents, the prevalence of asymptomatic bacteriuria is about 25-50% (Ia).
Asymptomatic bacteriuria does not require treatment in postmenopausal women apart from some exceptions (A- Ia).

5.4. Otherwise healthy young men
Generally UTIs in men are complicated, but occasionally there are acute episodes of uncomplicated UTI (IIb).

UTIs in men always need a differentiated diagnostic evaluation (A-GCP).

Asymptomatic bacteriuria in otherwise healthy young men usually does not require treatment (B-V).

5.5. Otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism
In otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism, UTIs can be assumed to be uncomplicated (B-IIa).

UTI in otherwise healthy patients with diabetes mellitus and unstable glycaemic metabolism can be problematic because of aggravated insulin resistance and an increasingly unstable glycaemic metabolism (III).

With unstable glycaemic metabolism and with manifest diabetic complications UTIs are consi-dered to be complicated (A-V).

6. DIAGNOSTICS OF UTIs

6.1. Introduction
A diagnosis based on clinical criteria alone is associated with an error rate up to one third (Ia).
Even the use of low-threshold test instruments such as urine dipsticks, can improve the diagno-otic accuracy only to a limited extent (Ia).

6.2. Medical History
All patients, in which a UTI is to be confirmed or ruled out, have to undergo a thorough medical history of sym-poms, diagnostic findings and risk factors, e.g. dysuria, frequency, urgency, in -creased or reoccurring incontinence, gross haematuria, suprapubic pain, flank pain, fever, urine smell and/or cloudy urine, previous UTI, conspicuous vagi-nalis discharge or vaginal irritation, as well as risk factors for a complicated progress (A-Ia).

Type and frequency of complications may differ in indi-vidual groups of patients. Therefore group-specific diagno-stic strategies should be used (B-IIb).

6.3. Diagnostics in different groups of patients
6.3.1. Diagnostics in otherwise healthy, non-pregnant premenopausal women
6.3.1.1. Acute uncomplicated cystitis in otherwise healthy, non-pregnant premenopausal women

An uncomplicated acute cystitis can be assumed in otherwise healthy non-pregnant premeno-pausal women with typical acute complaints, such as dysuria, frequency, urgency and absence of vaginalis discharge, if pyelonephritis and complicated UTI are unlikely on the basis of medical histo-ry. Urinalysis and further diagnostics are unnecessary (C-Ia).

At the first manifestation of an acute UTI, or if the pa-tient is unknown to the physician, symptom related investi-gations with medical history, physical examination and uri-nalysis (including mi-croscopy, if applicable) should al-ways be performed (B-V).

6.3.1.2. Acute uncomplicated pyelonephritis in otherwise healthy, non-pregnant premeno-pausal women

In diagnostics of acute uncomplicated pyelonephritis in otherwise-healthy non-pregnant women, the medical histo-ry follows the general principles (see 3.2). In addition, a physical examination and urinalysis including culture should be performed (A-V).
In order to rule out complicating factors further examina-tions (e.g., ultrasound) are necessary (A-V).

6.3.1.3. Asymptomatic bacteriuria in otherwise healthy, non-pregnant, premenopausal women
Screening for asymptomatic bacteriuria in otherwise healthy, non-pregnant women is not neces-sary because usually it has no therapeutic consequences (A-Ia).

6.3.2. Diagnostics in otherwise healthy pregnant women without risk factors
6.3.2.1. Acute uncomplicated cystitis in otherwise healthy pregnant women without risk factors
Diagnostics of acute uncomplicated cystitis in otherwise healthy pregnant women are performed the same way as in non-pregnant patients regarding medical history. However, physical examination and urinalysis including urine culture are always necessary (A-V). During pregnancy bacteriological eradication should be verified by urine culture after antibiotic therapy (A-V).

6.3.2.2. Acute uncomplicated pyelonephritis in otherwise healthy pregnant women without risk factors

Diagnostics of acute pyelonephritis in otherwise healthy pregnant women are similar to diagnostics of non-pregnant patients (A-V). Physical examination and urinalysis including a urine culture should be performed in each case (A-V).

Even in case of suspected pyelonephritis an ultrasound of the kidneys and urinary tract should be made in addition (A-V).

During pregnancy bacteriological eradication should be verified by urine culture after antibiotic therapy (A-V).

6.3.2.3 Asymptomatic bacteriuria in otherwise healthy pregnant women without risk factors

As the therapy of asymptomatic bacteriuria in pregnancy is recommended (A-IIb), a screening via urinalysis including urine culture should be performed, preferably at the end of the first trimester (A-V).

The use of dipsticks only is insufficient to diagnose asymptomatic bacteriuria (A-IV).

Bacterial eradication should be verified by additional urine culture after therapy (A-V).

6.3.3. Diagnostics in otherwise healthy postmenopausal women

6.3.3.1. Acute uncomplicated cystitis in otherwise healthy postmenopausal women

Diagnostics of acute uncomplicated cystitis in otherwise healthy postmenopausal women is made also by medical history as in otherwise healthy premenopausal woman (A-V).

At the first manifestation of an acute UTI, or if the patient is unknown to the physician, symptom related investigations with medical history, physical examination and urinalysis (including microscopy, if applicable) should always be performed (B-V).

To what extent additional diagnostic procedures (e.g. physical investigation, urinalysis including urine culture) are required in this group, has not yet been proven by convincing studies (D-V).

6.3.3.2. Acute uncomplicated pyelonephritis in otherwise healthy postmenopausal women

Diagnostics of acute uncomplicated pyelonephritis in otherwise healthy postmenopausal women follows general principles concerning medical history (see 3.2). In addition, a physical examination and urinalysis including urine culture is indicated (A-V).

In case of suspected urine transport disorders (e.g. increased residual urine) the exclusion of complicating factors by advanced examinations (e.g. ultrasound) is necessary (A-V).

6.3.3.3. Asymptomatic bacteriuria in otherwise healthy postmenopausal women

Screening for asymptomatic bacteriuria in otherwise healthy postmenopausal women is not necessary because usually no therapeutic consequences result (A-Ia).

6.3.4. Diagnostics in otherwise healthy young men

6.3.4.1/2. Acute uncomplicated cystitis and pyelonephritis in otherwise healthy young men

Complicating factors must be ruled out if the diagnosis of uncomplicated UTI (cystitis or pyelonephritis) is made in men (A-IIb).

In cases of suspected urethritis the diagnostics of urethritis are indicated (A-V).

Besides medical history a physical (including a rectal) examination is indicated in otherwise healthy young men (A-V).

Diagonstics of UTI in otherwise healthy young men should be confirmed by urinalysis including urine culture (A-V).

Diagnostics by dipsticks only are not recommended because of insufficient sensitivity and specificty (B-IIb).

6.3.4.3. Asymptomatic bacteriuria in otherwise healthy young men

Screening for asymptomatic bacteriuria in otherwise healthy men is not necessary, because detection of pathogens usually remains without therapeutic consequences (A-V).

6.3.5. Diagnostics in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

6.3.5.1. Acute uncomplicated cystitis in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

If there are typical and acute complaints such as dysuria, frequency, urgency, and if pyelonephritis-tis and complicated UTI are unlikely based on the patients medical history, an uncomplicated acute cystitis should be assumed in otherwise healthy diabetic women with stable glycaemic metabolism (HbA1c <7.5%, no predisposition to hypo- or hyperglycaemia, no diabetic nephropathy). (B-V).

At the first manifestation of an acute UTI, or if the patient is unknown to the physician, symptom related investigations with medical history, physical examination and urinalysis (including microscopy, if applicable) should always be performed (B-V).

To what extent additional diagnostic procedures (e.g. physical investigation, urinalysis including urine culture) are required in this group, has not yet been proved by convincing studies (D-V).

In otherwise healthy diabetic men diagnostics should be performed as described under 6.3.4.1/2. (A-V)

6.3.5.2. Acute uncomplicated pyelonephritis in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

Diagnostics of acute uncomplicated pyelonephritis in otherwise healthy diabetic women with stable glycaemic metabolism follows general principles concerning medical history (see 3.2). In addition, a physical examination and urinalysis including urine culture is indicated (A-V).

Advanced examinations (e.g. ultrasound) are necessary to rule out complicating factors (A-V).

In otherwise healthy diabetic men diagnostics should be performed as described under 6.3.4.1/2. (A-V).

6.3.5.3. Asymptomatic bacteriuria in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

Screening for asymptomatic bacteriuria in otherwise healthy diabetic patients with stable glycaemic metabolism is not necessary because usually therapeutic consequences do not result (A-Ia).

6.4. Urinalysis

The gold standard for diagnosis of UTI is in case of a positive medical history and typical symptoms, the urinalysis in-
cluding a quantitative urine culture and its assessment (A-Ia).

The so far usual typical criteria for microbiological diagnosis of UTI includes the detection of bacterial counts of > 105 colony forming units (CFU) / ml of typical uropathogens (A-Ia). However, sensitivity and specificity respectively positive / negative predictive values for an UTI are already relatively high with bacterial counts from 103 to 104 CFU / ml in case of mononinfec-tions (i.e. one species of bacteria only) of typical uropathogens (A-Ia).

In urine cultures from suprapubic bladder puncture specimens, any count of uropathogens has a clinical relevance. Therefore urine cultures from suprapubic bladder punctures should be pre pared in such a way, that already bacterial counts of 102 CFU/ml can be detected reliably (at least 10 identical colonies) (B-Ia).

6.4.2.6. Urinary diagnostic procedures

Urine samples for microbiological diagnostics with culture should be processed without delay. In case of sampling in the afternoon or during the night urine should be kept re-frigerated at 2-8°C in case the sample cannot be transported or processed immediately. This urine sample must be pro-cessed the following day. Reports of such urine samples should be labelled that storage of urine can change the number of pathogens (A-GCP).

6.4.2.4. Urine culture

The quantitative urine culture with identification of pathogens (<104/ml) is not possible because of method related reasons (A-Ia).

6.4.2.5. Imaging diagnostics and endoscopy

For clarification of complicating factors ultrasound of the kidneys and urinary tract is the pri-mary diagnostic imaging procedure (A-GCP). Additional imaging diagnostic procedures should be performed in case of specific clinical prob-lems (B-V).

Routine cystoscopy is not indicated in otherwise healthy women with recurrent UTI (A-Iib).

6.4.2.6. Differential diagnosis

In cases with unclear clinical symptoms, atypical complaints, non-conclusive urine analysis including negative urine culture, differential diagnosis should be considered at an early stage. (A-GCP).

UTI: Urinary tract infection

6.4.1. Urine sampling

Common recommendations with the goal to reduce contaminations are:
- spreading of the labia (B-IV)
- thorough cleansing of the urethral meatus of the women or the glans penis of the men with water (B-IV)
- collection of midstream urine (B-IV).

If only an exploratory urinalysis (e.g. dipsticks) is requi-red, collection of midstream urine instead of spontaneous urine and cleansing of the vaginal introitus or the glans pe-nis are unnecessary (C-IV). Nevertheless, advanced labora-tory-chemical and / or microbiological examinations requi-re an exact collection and processing of the urine, usually from midstream urine. Contaminations by urethral and/or surrounding flora are to be kept low (A-IV).

TABLE 2 – Indication for urine culture.

<table>
<thead>
<tr>
<th>A. Asymptomatic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>- leucocyturia, hematuria or a positive nitrit test in patients with specific risk factors (state after renal transplantation, vesicou-retal reflex)</td>
</tr>
<tr>
<td>- after completing the antibiotic therapy in pregnant women, men, of pyelonephritis or complicated urinary infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Symptomatic patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>- all patients with clinical suspicion of UTI, except in women with uncomplicated cystitis</td>
</tr>
<tr>
<td>- signs of recurrent UTI in outpatients</td>
</tr>
<tr>
<td>- signs of UTI with predisposing factors, e.g. complicated UTI in outpatients</td>
</tr>
<tr>
<td>- all signs of nosocomial UTI</td>
</tr>
<tr>
<td>- persisting symptoms under or after antibiotic therapy</td>
</tr>
<tr>
<td>- fever or sepsis of unknown origin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Targeted indications in special clinical cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- before and after urological interventions</td>
</tr>
<tr>
<td>- pregnancy</td>
</tr>
<tr>
<td>- immunosuppression</td>
</tr>
<tr>
<td>- neurogenic bladder voiding disorders, e.g. meningomylocele</td>
</tr>
<tr>
<td>- unclear abdominal complaints or flank pain</td>
</tr>
</tbody>
</table>

7. SPECTRUM OF PATHOGENS

Escherichia coli is the most causative pathogen of uncomplicated UTIs, followed by Staphylo-coccus saprophy-ticus, Klebsiella pneumoniae, and Proteus mirabilis. Other pathogens are rare (Ia). Enterococci are mostly found in mixed infections (Ic). Therefore, their pathogenicity in un-
complicated UTIs is uncertain.

TABLE 3. – Spectrum of pathogens in women with uncomplicated cystitis in Germany compared with nine other European countries and Brazil (ARESC study).24

<table>
<thead>
<tr>
<th>Germany</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>243</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>15</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>8</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>4</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>2</td>
</tr>
<tr>
<td>Other Enterobacteriaceae</td>
<td>5</td>
</tr>
<tr>
<td>Non Enterobacteriaceae</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>9</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>7</td>
</tr>
<tr>
<td>Other coagulase-negative staphylococci</td>
<td>14</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>317</td>
</tr>
</tbody>
</table>

TABLE 4. – Number and percentage of sensitive and resistant strains of Escherichia coli and of the entire spectrum of pathogens from female patients with uncomplicated cystitis in Germany for 9 antibiotics (CLSI criteria) (ARESC study) (Ia).25

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Germany</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>144</td>
<td>59.2%</td>
</tr>
<tr>
<td>Amoxicillin/Clavulan acid</td>
<td>215</td>
<td>88.8%</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>222</td>
<td>91.3%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>232</td>
<td>95.4%</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>180</td>
<td>74.0%</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>238</td>
<td>97.9%</td>
</tr>
<tr>
<td>Mecillinam</td>
<td>235</td>
<td>97.5%</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>220</td>
<td>90.5%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>232</td>
<td>95.4%</td>
</tr>
</tbody>
</table>

Figure 2. – Decision tree - diagnostics and therapy of symptomatic patients (clinical-microbiological path of diagnostics).
8. SUSCEPTIBILITY OF PATHOGENS

Susceptibility strongly depends on the substance. In the ARESPC study the susceptibility of Escherichia coli (total spectrum) was highest for fosfomycin trometamol with 97.9% (96.1%) followed by mecillinam with 97.5% (97.5%), ciprofloxacin with 95.4% (92.3%), nitrofurantoin with 95.4% (86.3%), cefuroxime, with 91.3% (89.2%), nalidixic acid with 90.5% (90.6%), amoxicillin/clavulanic acid with 88.8% (87.0%), cotrimoxazole 74.0% (73.9%) and ampicillin with 59.2% (56.6%).

In another German investigation² of urine cultures from uncomplicated and complicated UTIs in female patients from general practices the resistance rate of Escherichia coli against amoxicillin, amoxicillin/clavulan acid, oral cephalosporins (group 1 by PEG) and cotrimoxazole was between 25 and 40%. 9% of the isolates were resistant to fluoroquinolones. The resistance rate of Escherichia coli against nitrofurantoin (2%) and oral cephalosporins (group 1 by PEG) 3 (3%) was low. In elder patients with complicated UTIs the resistance rate of Escherichia coli against most antibiotics was significantly higher (2-5 fold).

9. ANTIBIOTIC THERAPY

9.1. Indication for an antibiotic therapy

If an uncomplicated UTI is limited to the bladder, even in recurrent episodes no serious complications are to be expected (Iic).

The basic intention of antibiotic therapy is to rapidly relieve clinical symptoms (B-V).

In acute uncomplicated cystitis an antibiotic therapy should be recommended (B-Ib) (1).

In acute uncomplicated pyelonephritis an effective antibiotic therapy should be applied as soon as possible. (A-Ic).

Asymptomatic bacteriuria increases the risk of infection in pregnant women and in patients with expected mucocutaneous trauamising interventions of the urinary tract. In these cases the patient should be screened for asymptomatic bacteriuria and treated if necessary (A-Ib).

9.2. Preferred form of therapy

An oral antibiotic therapy should be the preferred method of treatment (B-GCP).

For therapy of acute uncomplicated cystitis a short course therapy with an appropriate antibiotic should be possibly preferred (B-Ia).

9.3. Choice of antibiotics

Selecting an antibiotic the following criteria have to be considered:

- individual risk of the patient (A-GCP)
- spectrum of pathogens and susceptibility against antibiotics (A-IIa)
- effectiveness of antimicrobials (A-Ia)
- adverse effects from the drug (A-GCP)
- effects on the individual patients (collateral damage) and/or general public (epidemiological effects) bacterial resistance situation (A-IIc).

From the group of oral antibiotics or antibiotic classes basically appropriate for the therapy of UTI - aminopenicillins in combination with a betalactamase inhibitor, cephalosporins group 2 and 3 (by PEG), fluoroquinolones, fosfomycin trometamol, nitrofurantoin, pivmecillinam, trimethoprim or cotrimoxazole – the risk of microbiological "collateral damages" by selection of multiresistant pathogens or the risk of clostridium difficile-related colitis is highest with fluoroquinolones and cephalosporins (IIIb).

Regarding inevitable use of fluoroquinolones and/or cephalosporins for other indications, the clinical consequence of an increased resistance towards these substances should be assessed as more significant than that of previously mentioned antibiotics (B-V).

As long as there are therapeutic alternatives with comparable efficacy and acceptable adverse effects, fluoroquinolones and cephalosporins should not be used as antibiotics of the first choice in uncomplicated cystitis (B-V).

Physicians dealing with the therapy of UTI should get informed about the spectrum of pathogens and local changes in resistance patterns. Sources for these analyses are national studies, analyses of the physicians’ associated microbiological laboratories and the physicians’ own evaluations (B-IIa).

9.4. Antibiotic therapy

9.4.1. Aminopenicillins ± Beta-lactamase inhibitors

Ampicillin, the better absorbable ampicillinesters and amoxicillin can no longer be recom-mended for empiric therapy because of the low / high susceptibility / resistance patterns (A-IIa).

Aminopenicillins + betalactamase inhibitors are not the first choice for the empiric short course therapy of uncomplicated cystitis (A-Ib).

There are, however, no sufficient studies for the therapy of pyelonephritis (D).

9.4.2. Cephalosporins

There are only a few convincing studies for oral cephalosporins. But oral cephalosporins should not be used as antibiotics of first choice for empiric therapy of uncomplicated UTI (B-V).

In uncomplicated cystitis a 3-day course with cefpodoxime proxetil (100 mg bid ) is equivalent to a 3-day course with cotrimoxazole. Therefore cefpodoxime proxetil is an alternative in the treatment of uncomplicated cystitis when other antibiotics are unsuitable (B-Ib).

A 10-day therapy with cefpodoxime proxetil (200 mg bid) was clinically (not microbiologically) equivalent to a 10-day therapy with ciprofloxacin in uncomplicated pyelonephritis Therefore cefpodoxime proxetil can be considered an alternative in the treatment of uncomplicated pyelonephritis, when other antibiotics are unsuitable (C-Ib).

9.4.3. Fluoroquinolones

Fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin) are well effective in a 3-day treatment of uncomplicated cystitis (Ib). However, they are no longer recommended as antibiotic of the first choice for treatment of uncomplicated cystitis, since they are used (have to be used) in other indications and given that other antibiotics are available, which are exclusively used for the therapy of uncomplicated cystitis (B-V).

Fluoroquinolones at a sufficiently high dose - Ciprofloxacin 500-750 mg daily bid (Ib) or Levofloxacin 500-750mg qd (Ib) – are considered oral antibiotics of the first choice for empiric treatment of mild and moderate uncomplicated pyelonephritis, if the local resistance rate of Escherichia coli is <10% (A-V).

9.4.4. Fosfomycin

In clinical trials a single dose of fosfomycin trometamol was not inferior to cotrimoxazole, trimethoprim or nitrofurantoin in the empiric treatment of uncomplicated cystitis.
in otherwise healthy women (Ia).

Due to low resistance rates and due to low collateral damage fosfomycin trometamol is deemed to be a drug of the first choice in the empiric treatment of uncomplicated cystitis in otherwise healthy women (A-Ib).

In clinical trials with a single dose of fosfomycin trometamol in otherwise healthy women (A-Ib).

9.4.5. Nitrofurantoin

In clinical trials macrocrystalline nitrofurantoin (extended release form 100mg bid for 5 days) was as effective as a 3-day course with cotrimoxazole in the empiric treatment of uncomplicated cystitis (Ib).

Due to low resistance patterns and low collateral damage nitrofurantoin is a drug of choice in empiric treatment of uncomplicated cystitis in otherwise healthy women (A-Ib).

Nitrofurantoin was investigated in a short-term course of 3 days only against placebo. Prolonged treatment (3-7 days) showed better results (A-Ib).

9.4.6. Pivmecillinam (available in Austria and Scandinavia, not in Germany)

In clinical trials pivmecillinam (400 mg bid for 3 days) was clinically (not microbiologically) as effective as a 3-day course with norfloxacin in the empiric treatment of uncomplicated cystitis in women (Ib). In clinical trials women with uncomplicated cystitis were empirically more effectively treated with pivmecillinam at a dosage of 200 mg bid for 7 days than with pivmecillinam at a dosage of 400 mg bid for 3 days (Ib).

Due to low resistance rates and due to low collateral damage pivmecillinam is an antibiotic of the first choice for empiric treatment of uncomplicated cystitis in otherwise healthy women. The recommended duration of therapy (3-7 days) depends on the dosage (see Table 5) (A-Ib).

9.4.7. Trimethoprim mono or in combination with a sulfonamide

In the past cotrimoxazole (trimethoprim/sulfamethoxazole) and trimethoprim were the standard in empiric treatment of cystitis (Ia).

Due to existing resistance rates, which according to the ARESC study in Germany are > 20% for Escherichia coli and also for the total spectrum of pathogens, a higher failure rate is now to be expected (Ib). Therefore, cotrimoxazole and trimethoprim are recommended only as antibiotics of first choice for empiric treatment, if rates of resistance below 20% can be verified (B)(2).

10. ANTIBIOTIC THERAPY OF ACUTE UNCOMPLICATED UTI IN SPECIAL PATIENT GROUPS

10.1. Antibiotic therapy of acute uncomplicated UTI in otherwise healthy premenopausal women

10.1.1. Acute uncomplicated cystitis in otherwise healthy premenopausal women

In otherwise healthy premenopausal women with typical medical history and complaints of uncomplicated cystitis, a routine urine culture is unnecessary before therapy, as clinical cure is ex-pected within a few days and as no more consequences are drawn from the results of the urine cultu-

re (A-V).

At the first manifestation of an acute UTI, or if the patient is unknown to the physician symptom related investigations with medical history, physical examination and urinalysis (including mi-crosopy, if applicable) should always be performed (B-V).

To optimize this treatment strategy regular contemporary and local epidemiological studies of pathogen susceptibility are recommended, since pathogen susceptibility varies regionally and also changes with time (B-IIa).

Antibiotics of the first choice are fosfomycin trometamol, nitrofurantoin and pivmecillinam, because the susceptibility of Escherichia coli pathogens to these antibiotics is high and because they cause little collateral damage. These antibiotics are primarily used for the therapy of uncomplicated cystitis (A-Ib). Consensus 10/12 (2 abstentions – see minority vote of DEGAM).

Cotrimoxazole, trimethoprim, fluoroquinolones, cephalosporins and aminopenicillins in combination with a beta-lactamase-inhibitor should only be used alternatively in empiric treatment, if local resistance patterns (<20%) permit and first choice drugs cannot be used (B-V).

Monitoring the efficacy of treatment of uncomplicated cystitis in otherwise healthy premenopausal women is unnecessary if they had become asymptomatic (B-V).

If therapy fails (within 2 weeks), non-compliance of patients, resistant pathogens or so far unre-cognized risk factors should be considered. In these cases, differentiated instructions and a physi-cal examination of the patient; a urinalysis including urine culture; and possibly a switch of the antibiotic regimen are indicated before starting the next attempt of antibiotic treatment (B-V).

A clinical recurrence may be caused by the same or a different pathogen. As frequently a change of resistance patterns is observed, urinalysis including urine culture is recommended (B-IIa).

Table 5 – Recommended short-term course for uncomplicated cystitis in otherwise healthy premenopausal women (without risk factors).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic of first choice (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosfomycin trometamol</td>
<td>3000mg qd</td>
<td>1 d</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50mg q6h</td>
<td>7 d</td>
</tr>
<tr>
<td>Nitrofurantion RT</td>
<td>100mg bid</td>
<td>5 d</td>
</tr>
<tr>
<td>Pivmecillinam*</td>
<td>200mg bid</td>
<td>7 d</td>
</tr>
<tr>
<td>Pivmecillinam*</td>
<td>400mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>Antibiotic of second choice (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>Ciprofloxacin RT</td>
<td>500mg qd</td>
<td>3 d</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>250mg qd</td>
<td>3 d</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>200mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>Cefpodoxime proxetil</td>
<td>100mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>If local resistance patterns are known (Escherichia coli resistance rate &lt; 20%) (B)(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>160/800mg bid</td>
<td>3 d</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>200mg bid</td>
<td>5 d</td>
</tr>
</tbody>
</table>

RT= slow releasing form (= macrocrystalline form) *available in Austria and Scandinavia, not in Germany.

10.1.2. Acute uncomplicated pyelonephritis in otherwise healthy premenopausal women

Pyelonephritis with mild and moderate symptoms in
otherwise healthy premenopausal women should be treated with oral antibiotics (B-Ib). In severe infections with systemic side effects, like nausea, vomiting, and/or cardiovascular instability, therapy should be started with high dose parenteral antibiotics (B-Ib)(Figure 5).

In mild or moderate pyelonephritis with clinically uneventful course 2 weeks of treatment are generally sufficient in otherwise healthy premenopausal women. With fluoroquinolones, the therapy can be shortened to 7-10 days. If used at higher doses, e.g. Levofloxacin 750 mg qd, the treatment duration can even be reduced to 5 days (B-Ib).

Fluoroquinolones should be considered as first choice antibiotics if the local Escherichia coli resistance rate is <10% (B-Ib).

Cefpodoxime proxetil should be considered in situations where other antibiotics e.g. fluoroquinolones cannot be applied (B-Ib).

Cotrimoxazole should not be used anymore for empiric therapy of pyelonephritis (A-Ib). But Cotrimoxazole can be given as an oral sequence therapy after initial parenteral therapy, if patho-gens are tested susceptible for cotrimoxazole (C-Ib). Trimethoprim has not been studied in this context.

Table 6. – Recommended empiric antibiotic therapy of uncomplicated pyelonephritis in otherwise healthy premenopausal women (without risk factors).

<table>
<thead>
<tr>
<th>Antibiotic of first choice (A)</th>
<th>Daily dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin 1</td>
<td>500-750 mg bid</td>
<td>7-10 d</td>
</tr>
<tr>
<td>Ciprofloxacin RT</td>
<td>1000 mg qd</td>
<td>7-10 d</td>
</tr>
<tr>
<td>Levofloxacin 1</td>
<td>(250-) 500 mg qd</td>
<td>7-10 d</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg qd</td>
<td>5 d</td>
</tr>
</tbody>
</table>

Antibiotic of second choice (B)

1) Low doses studied, high dosage recommended by experts
2) Not investigated in convincing clinical studies.
3) Primarily for Gram-positive pathogens
4) If Escherichia coli resistance is <10%

If susceptibility of pathogens is confirmed (B)

(1) Similar clinical efficacy, microbiologically not equivalent with fluoroquinolones

Cefpodoxime proxetil 200 mg bid 10 d
Cefditoren pivoxil 400 mg qd 10 d
Cefditoren pivoxil 200 mg bid 10 d

If susceptibility of pathogens is confirmed (B)

(Not for empiric therapy)

Cotrimoxazole 160/800 mg bid 14 d
Amoxicillin/Clavulanic acid 0.875/0.125 g bid 14 d
Amoxicillin/Clavulanic acid 0.5/0.125 g tid 14 d

10.1.3. Asymptomatic bacteriuria in otherwise healthy premenopausal women

Asymptomatic bacteriuria in otherwise healthy premenopausal women is not associated with adverse outcomes. Therefore neither screening nor therapy are generally necessary (A-Ia).

10.2. Antibiotic therapy of acute uncomplicated UTI in otherwise healthy pregnant women without risk factors

When selecting drugs possible adverse reactions on the embryo/fetus have to be taken into account. Mainly penicillins, cephalosporins or fosfomycin trometamol should be considered (A-GCP).

Asymptomatic bacteriuria and symptomatic UTI in pregnancy have to be treated with antibiotics to avoid serious consequences for mother and child (A-Ia).

10.2.1. Acute uncomplicated cystitis in otherwise healthy pregnant women without risk factors

Short-term therapy of acute cystitis in pregnant women is not as well investigated as in non-pregnant women. For treatment fosfomycin trometamol (single dose), pivmecillinam, oral cephalosporins of group 2 or 3 are primarily recommended (B-IIa).

10.2.2. Acute uncomplicated pyelonephritis in otherwise healthy pregnant women without risk factors

During pregnancy inpatient treatment of pyelonephritis has to be considered (A-V).

For empiric treatment cephalosporins of group 2 and 3 are mainly recommended (B-V).

After therapy of pyelonephritis a follow-up urine culture is necessary to demonstrate success, because asymptomatic bacteriuria has to be treated as well (A-Ia).

10.2.3. Asymptomatic bacteriuria in otherwise healthy pregnant women without risk factors

Treatment of asymptomatic bacteriuria during pregnancy should be initiated according to resistance patterns, when pathogens are identified and their susceptibility is known. (B-V)

10.3. Antibiotic therapy of acute uncomplicated UTI in otherwise healthy postmenopausal women

The short-term therapy of acute cystitis in postmenopausal women is not as well established as in premenopausal woman. Recent studies, however, demonstrate the possibility of short-term therapy (C-Ib).

Selection and dosage of antibiotics comply with treatment regimens of premenopausal women (B-V).

10.3.1. Acute uncomplicated cystitis in otherwise healthy postmenopausal women

The short-term therapy of acute cystitis in postmenopausal women is not as well established as in premenopausal woman. Recent studies, however, demonstrate the possibility of short-term therapy (C-Ib).

Selection and dosage of antibiotics comply with treatment regimens of premenopausal women (B-V).

10.3.2. Acute uncomplicated pyelonephritis in otherwise healthy postmenopausal women

For the antibiotic treatment of acute uncomplicated pyelonephritis in postmenopausal women an approach similar to the treatment of premenopausal women is recommended.
Figure 3. – Clinical management of acute pyelonephritis in female adult patients
BLI = betalactamase inhibitor; TMP = Trimethoprim; SMX = Sulfamethoxazole.
**10.4. Antibiotic therapy of acute UTI in otherwise healthy young men**

**10.4.1. Acute uncomplicated cystitis in otherwise healthy young men**

For the empirical oral therapy of acute uncomplicated cystitis in young men, the same antibiotics are recommended as in women (Table 4), with the exceptions of fosfomycin trometamol (single dose), pivmecillinam and nitrofurantoin (B-V).

**10.4.2. Acute uncomplicated pyelonephritis in otherwise healthy young men**

For the empirical oral therapy of mild and moderate acute uncomplicated pyelonephritis in young men fluoroquinolones are recommended as first choice, if the local resistance rate of Escherichia coli is < 10% (A-IIb).

Duration of therapy is usually 7-10 days (B-IIa).

**10.4.3. Asymptomatic bacteriuria in otherwise healthy young men**

Also in men asymptomatic bacteriuria is probably not associated with adverse outcomes. Therefore therapy is generally unnecessary if complicating factors are excluded (B-V).

**10.5. Antibiotic therapy of acute UTI in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

**10.5.1. Acute uncomplicated cystitis in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

In patients with uncomplicated UTI and diabetes mellitus, the spectrum of pathogens does not differ significantly from UTI in patients without diabetes mellitus. The predominant species is Escherichia coli (A-Ia).

Acute uncomplicated cystitis in patients with diabetes mellitus and stable glycaemic metabolism (HbA1c <7.5%, no predisposition to hypo- or hyperglycaemia, no diabetic nephropathy) should be treated in the same way as corresponding UTIs in patients without diabetes mellitus (B-V).

In acute uncomplicated cystitis in patients with diabetes mellitus and stable glycaemic metabolism a short-term antimicrobial therapy is justified (C-V).

In severe insulin resistance, threatening organ complications and a tendency to metabolic de-compensation inpatient treatment should be considered (A-V).

**10.5.2. Acute uncomplicated pyelonephritis in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

Antimicrobial treatment of otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism (HbA1c <7.5%, no predisposition to hypo- or hyperglycaemia, diabetic nephropathy) is the same as treatment in patients without diabetes mellitus. Controls of metabolic parameters, however, are necessary. The duration of antimicrobial therapy should depend on the clinical course of infection (B-V).

**10.5.3. Asymptomatic bacteriuria in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

Asymptomatic bacteriuria in otherwise healthy postmenopausal women is apparently not associated with adverse outcomes. Therefore neither screening nor therapy are generally necessary (A-IIb).

**REFERENCES**


