

# **S-3 Guideline AWMF-Register-Nr. 043/044**

## **Urinary Tract Infections**

### **Epidmiology, Diagnostics, Therapy and Management of Uncomplicated Bacterial Community Acquired Urinary Tract Infections in Adults**

**Creation date** 2010  
**Next scheduled review** 2015

**Short version 17 June 2010**

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#### **Acknowledgement**

Prof. Dr. Truls E. Bjerklund Johansen (Denmark), Prof. Dr. Frank Buntinx (Belgium), Prof. Dr. Geert Jan Dinant (Netherlands), Prof. Dr. Ellen Stobberingh (Netherlands), Prof. Dr. Arjana Tambic Andrasevic (Croatia), and Dr. Björn Wullt (Sweden) is thanked for the critical review of the manuscript.

Prof. Dr. Ina Kopp, clearing house of Guidelines of the Association of Scientific Medical Societies (AWMF), is thanked for the coordination and moderation, and Dr. Cordula Lebert for assistance with manuscript preparation.

# Short version

## Preliminary note

The 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.

## 1. Definition of uncomplicated urinary tract infections (UTIs)

1.a. A UTI is classified to be uncomplicated, if there are no relevant functional, anatomical or significant renal dysfunctions and no relevant comorbidities in the urinary tract favoring UTI or serious complications (A-V). Consensus 12/12.

1.b. A lower UTI (cystitis) is assumed if the symptoms are limited to the lower urinary tract, e.g., dysuria, urgency, frequency, suprapubic pain (A-V). Consensus 12/12.

1.c. An upper UTI (pyelonephritis) is assumed, if the symptoms comprise for instance flank pain, costovertebral angle tenderness and/or fever ( $> 38^{\circ}\text{C}$ ) (A-V). Consensus 10/12 (2 abstentions).

1.d. A clinically symptomatic UTI is differentiated from an asymptomatic bacteriuria (A). The term "asymptomatic urinary tract infection" should not be used (B-V). Consensus 12/12.

1.e. Recurrent UTI is assumed if a recurrence rate of  $> 2$  symptomatic episodes per six months or  $> 3$  symptomatic episodes per year exist (B-V). Consensus 12/12.

## 2. Groups of patients

2.a. Patients with uncomplicated UTI should be discerned into different groups with regard to diagnostic procedure and therapy (B-V). Consensus 12/12.

- 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

## **2.1. Otherwise healthy, non-pregnant premenopausal women**

**2.1.a.** In otherwise healthy, non-pregnant women the following factors increase the risk for UTI (**A**). Consensus 12/12.

- 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**)

**2.1.b.** The incidence of cystitis and pyelonephritis is greater in women than in men in this age group (**IIb**). Consensus 12/12.

**2.1.c.** 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**). Consensus 11/12 (1 abstention).

## **2.2. Otherwise healthy pregnant women without risk factors**

**2.2.a.** UTI and asymptomatic bacteriuria are more frequent in pregnancy (**Ila**).

**2.2.b.** The spectrum of pathogens and the bacterial resistance patterns are similar to non-pregnant premenopausal women (**Ila**).

**2.2.c.** The rate of pyelonephritis, compared to non pregnant women is increased (**Ila**).

**2.2.d.** There seem to be correlations between UTI and asymptomatic bacteriuria in pregnancy and preterm delivery, reduced birth weight, increased neonatal mortality and preeclampsia (**IIb**).

## **2.3. Otherwise healthy postmenopausal women**

**2.3.a.** 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 colonization 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**).

**2.3.b.** According to an American epidemiological study 6.7 episodes of UTI are expected per 100 person years in postmenopausal diabetic women (**IIb**).

2.3.c. There are epidemiological studies on the incidence of cystitis and pyelonephritis in postmenopausal women (IIb).

2.3.d. For female nursing home residents, the prevalence of asymptomatic bacteriuria is about 25-50% (Ia).

2.3.e. Asymptomatic bacteriuria does not require treatment in postmenopausal women apart from some exceptions (A-Ia). Consensus 11/12 (1 abstention).

## 2.4. Otherwise healthy young men

2.4.a. Generally UTIs in men are complicated, but occasionally there are acute episodes of uncomplicated UTI (IIb). Consensus 12/12.

2.4.b. UTIs in men always need a differentiated diagnostic evaluation (A-GCP). Consensus 12/12.

2.4.c. Asymptomatic bacteriuria in otherwise healthy young men usually does not require treatment (B-V). Consensus 11/12 (1 abstention).

## 2.5. Otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism

2.5.a. In otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism, UTIs can be assumed to be uncomplicated (B-IIa). Consensus 12/12.

2.5.b. 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). Consensus 12/12.

2.5.c. With unstable glycaemic metabolism and with manifest diabetic complications UTIs are considered to be complicated (A-V). Consensus 12/12.

# 3. Diagnostics of UTIs

## 3.1. Introduction

3.1.a. A diagnosis based on clinical criteria alone is associated with an error rate up to one third (Ia). Consensus 12/12.

3.1.b. Even the use of low-threshold test instruments such as urine dipsticks, can improve the diagnostic accuracy only to a limited extent (Ia). Consensus 11/12 (1 abstention).

## **3.2. Medical History**

**3.2.a.** All patients, in which a UTI is to be confirmed or ruled out, have to undergo a thorough medical history of symptoms, diagnostic findings and risk factors, e.g. dysuria, frequency, urgency, increased or reoccurring incontinence, gross haematuria, suprapubic pain, flank pain, fever, urine smell and/or cloudy urine, previous UTI, conspicuous vaginalis discharge or vaginal irritation, as well as risk factors for a complicated progress (**A-Ia**). Consensus 12/12.

**3.2.b.** Type and frequency of complications may differ in individual groups of patients. Therefore group-specific diagnostic strategies should be used (**B-IIb**). Consensus 12/12

## **3.3. Diagnostics in different groups of patients**

### **3.3.1. Diagnostics in otherwise healthy, non-pregnant premenopausal women**

#### **3.3.1.a. Acute uncomplicated cystitis in otherwise healthy, non-pregnant premenopausal women**

An uncomplicated acute cystitis can be assumed in otherwise healthy non-pregnant premenopausal 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 history. Urinalysis and further diagnostics are unnecessary (**C-Ia**). Consensus 12/12.

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**). Consensus 12/12.

#### **3.3.1.b. Acute uncomplicated pyelonephritis in otherwise healthy, non-pregnant premenopausal women**

In diagnostics of acute uncomplicated pyelonephritis in otherwise-healthy non-pregnant women, the medical history follows the general principles (see 3.2). In addition, a physical examination and urinalysis including culture should be performed (**A-V**). Consensus 12/12.

In order to rule out complicating factors further examinations (e.g., ultrasound) are necessary (**A-V**). Consensus 12/12.

#### **3.3.1.c. Asymptomatic bacteriuria in otherwise healthy, non-pregnant, premenopausal women**

Screening for asymptomatic bacteriuria in otherwise healthy, non-pregnant women is not necessary because usually it has no therapeutic consequences (**A-Ia**). Consensus 11/12. (1 abstention).

### **3.3.2.       Diagnostics in otherwise healthy pregnant women without risk factors**

#### **3.3.2.a.       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). Consensus 12/12.

During pregnancy bacteriological eradication should be verified by urine culture after antibiotic therapy (A-V). Consensus 12/12.

#### **3.3.2.b.       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). Consensus 12/12.

Physical examination and urinalysis including a urine culture should be performed in each case (A-V). Consensus 12/12.

Even in case of suspected pyelonephritis an ultrasound of the kidneys and urinary tract should be made in addition (A-V). Consensus 12/12.

During pregnancy bacteriological eradication should be verified by urine culture after antibiotic therapy (A-V). Consensus 12/12.

#### **3.3.2.c       Asymptomatic bacteriuria in otherwise healthy pregnant women without risk factors**

As the therapy of asymptomatic bacteriuria in pregnancy is recommended (A-Ib), a screening via urinalysis including urine culture should be performed, preferably at the end of the first trimester (A-V). Consensus 12/12.

The use of dipsticks only is insufficient to diagnose asymptomatic bacteriuria (A-IV). Consensus 12/12.

Bacterial eradication should be verified by additional urine culture after therapy (A-V). Consensus 12/12.

### **3.3.3. Diagnostics in otherwise healthy postmenopausal women**

#### **3.3.3.a. 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). Consensus 12/12.

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). Consensus 12/12.

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). Consensus 12/12.

#### **3.3.3.b. 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). Consensus 12/12.

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). Consensus 12/12.

#### **3.3.3.c. 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). Consensus 11/12 (1 abstention).

### **3.3.4. Diagnostics in otherwise healthy young men**

#### **3.3.4.a/b 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). Consensus 12/12.

In cases of suspected urethritis the diagnostics of urethritis are indicated (A-V). Consensus 12/12.

Besides medical history a physical (including a rectal) examination is indicated in otherwise healthy young men (A-V). Consensus 12/12.

Diagnostics of UTI in otherwise healthy young men should be confirmed by urinalysis including urine culture (A-V). Consensus 12/12.

Diagnostics by dipsticks only are not recommended because of insufficient sensitivity and specificity (B-IIb). Consensus 12/12

#### **3.3.4.c. 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). Consensus 11/12 (1 abstention).

#### **3.3.5. Diagnostics in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

##### **3.3.5.a. 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 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). Consensus 12/12.

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). Consensus 12/12.

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). Consensus 12/12.

In otherwise healthy diabetic men diagnostics should be performed as described under 3.3.4. a/b. (A-V) Consensus 12/12.

##### **3.3.5.b. 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). Consensus 12/12.



Advanced examinations (e.g. ultrasound) are necessary to rule out complicating factors (A-V). Consensus 12/12.

In otherwise healthy diabetic men diagnostics should be performed as described under 3.3.4. a/b. (A-V). Consensus 11/12 (1 abstention).

### **3.3.5.c. 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). Consensus 11/12 (1 abstention).

## **3.4. Urinalysis**

The gold standard for diagnosis of UTI is in case of a positive medical history and typical symptoms, the urinalysis including a quantitative urine culture and its assessment (A-Ia). Consensus 12/12.

The so far usual typical criteria for microbiological diagnosis of UTI includes the detection of bacterial counts of  $\geq 10^5$  colony forming units (CFU) / ml of typical uropathogens (A-Ia). Consensus 11/12 (1 abstention).

However, sensitivity and specificity respectively positive / negative predictive values for an UTI are already relatively high with bacterial counts from  $10^3$  to  $10^4$  CFU / ml in case of mono-infections (i.e. one species of bacteria only) of typical uropathogens (A-Ia). Consensus 12/12.

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 prepared in such a way, that already bacterial counts of  $10^2$  CFU/ml can be detected reliably (at least 10 identical colonies) (B-Ia). Consensus 12/12.

### **3.4.1. Urine sampling**

Common recommendations with the goal to reduce contaminations are (Consensus 12/12):

- 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 required, collection of midstream urine instead of spontaneous urine and cleansing of the vaginal introitus or the glans penis are unnecessary (C-IV). Consensus 11/12 (1 abstention).

Nevertheless, advanced laboratory-chemical and / or microbiological examinations require 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). Consensus 12/12.

### 3.4.2. 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 refrigerated at 2 – 8°C in case the sample cannot be transported or processed immediately. This urine sample must be processed the following day. Reports of such urine samples should be labelled that storage of urine can change the number of pathogens (A-GCP). Consensus 12/12.

#### 3.4.2.a. Urine dipsticks

Also a combination of clinical symptoms and negative results of dipsticks does not completely exclude a diagnosis of UTI (A-IIb). Consensus 12/12.

In a typical case of medical history (dysuria, frequency, urgency, exclusion of pathological vaginal discharge) the probability of a UTI is so high that the additional use of dipsticks can only marginally improve the diagnostic accuracy (A-Ia). Consensus 12/12.

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). Consensus 12/12.

#### 3.4.2.b. Urine microscopy

With appropriate experience in urine microscopy UTI can be excluded to a large extent (B-Ia). Consensus 12/12.

Centrifugation of urine for the microscopic detection of bacteria does not improve the accuracy of diagnosis (A-Ib). Consensus 12/12.

The lack of microscopic evidence of leukocytes excludes a UTI (B-IIIb). Consensus 12/12.

#### 3.4.2.c. Dip slide culture

Bacteriuria with higher numbers of pathogens ( $\geq 10^4$ /ml) can be excluded by a dip slide culture (A-Ia). Consensus 12/12.

The exclusion of bacteriuria with lower numbers of pathogens ( $<10^4$ /ml) is not possible because of method related reasons (A-Ia). Consensus 12/12.

### 3.4.2.d. Urine culture

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 refrigerated at 2 – 8°C in case the sample cannot be transported or processed immediately. This urine sample must be processed the following day. Reports of such urine samples should be labelled that storage of urine can change the number of pathogens (A-GCP). Consensus 12/12.

The quantitative urine culture with identification of pathogens and susceptibility testing is essential for targeted and successful therapy especially in cases of complicated and recurrent UTI (A-V). Consensus 12/12.

**Tabelle K1 Indication for urine culture**

<b>A. Asymptomatic patient</b>
<ul style="list-style-type: none"><li>- leucocyturia, hematuria or a positive nitrit test in patients with specific risk factors (state after renal transplantation, vesicoureteral reflux)</li><li>- after completing the antibiotic therapy in pregnant women, men, of pyelonephritis or complicated urinary infections</li></ul>
<b>B. Symptomatic patient</b>
<ul style="list-style-type: none"><li>- all patients with clinical suspicion of UTI, except in women with uncomplicated cystitis</li><li>- signs of recurrent UTI in outpatients</li><li>- signs of UTI with predisposing factors, e.g. complicated UTI in outpatients</li><li>- all signs of nosocomial UTI</li><li>- persisting symptoms under or after antibiotic therapy</li><li>- fever or sepsis of unknown origin</li></ul>
<b>C. Targeted indications in special clinical cases</b>
<ul style="list-style-type: none"><li>- before and after urological interventions</li><li>- pregnancy</li><li>- immunosuppression</li><li>- neurogenic bladder voiding disorders, e.g. meningomyelocele</li><li>- unclear abdominal complaints or flank pain</li></ul>

### 3.4.2.e. Imaging diagnostics and endoscopy

For clarification of complicating factors ultrasound of the kidneys and urinary tract is the primary diagnostic imaging procedure (A-GCP). Consensus 12/12.

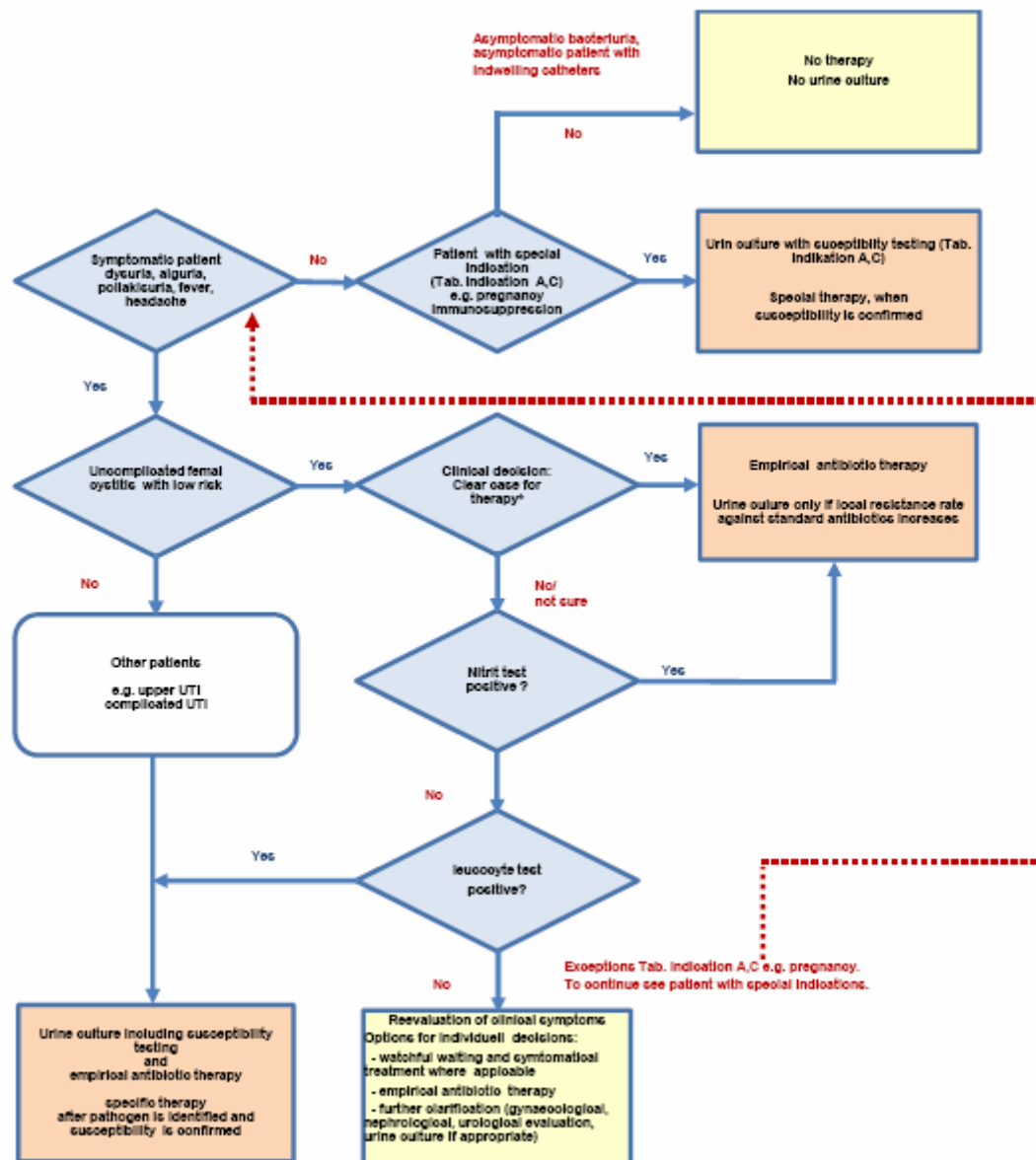
Additional imaging diagnostic procedures should be performed in case of specific clinical problems (B-V). Consensus 12/12.

Routine cystoscopy is not indicated in otherwise healthy women with recurrent UTI (A-IIb). Consensus 12/12.

### 3.4.2.f. 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). Consensus 12/12

**Figure K1 Decision tree - Diagnostics and therapy of symptomatic patients (clinical- microbiological path of diagnostics)**



UTI: Urinary tract infection, test: dipstick=

\* 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

## 4. Spectrum of pathogens

**Table K2** Spectrum of pathogens in women with uncomplicated cystitis in Germany compared with nine other European countries and Brazil (ARESC study)

Pathogen	Germany		Total	
	n	%	n	%
Escherichia coli	243	76.7	2,315	76.7
Proteus mirabilis	15	4.7	104	3.4
Klebsiella pneumoniae	8	2.5	107	3.5
Enterobacter spp.	4	1.3	34	1.1
Citrobacter spp.	2	0.6	29	1.0
Other Enterobacteriaceae	5	1.6	36	1.2
Non Enterobacteriaceae	0	0	6	0.2
Staphylococcus saprophyticus	9	2.8	108	3.5
Staphylococcus aureus	7	2.2	32	1.1
Other coagulase-negative staphylococci	14	4.4	68	2.3
Enterococcus spp.	8	2.5	123	4.1
Streptococcus spp.	2	0.6	56	1.9
Total	317	100	3,018	100

**Escherichia coli** is the most causative pathogen of uncomplicated UTIs, followed by **Staphylococcus saprophyticus**, **Klebsiella pneumoniae**, and **Proteus mirabilis**. Other pathogens are rare (la).

**Enterococci** are mostly found in mixed infections (lc). Therefore, their pathogenicity in uncomplicated UTIs is uncertain.

## 5. Susceptibility of pathogens

**Table K3** 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) (la).

	Escherichia coli				Total bacterial spectrum			
	susceptible		resistant		susceptible		resistant	
	n	%	n	%	n	%	n	%
Ampicillin	144	59.2%	85	34.9%	157	56.6%	105	37.9%
Amoxicillin/Clavulan acid	215	88.8%	3	1.2%	241	87.0%	9	3.2%
Cefuroxime	222	91.3%	1	0.4%	274	89.2%	7	2.2%
Ciprofloxacin	232	95.4%	11	4.5%	291	92.3%	21	6.6%
Cotrimoxazole	180	74.0%	63	25.9%	227	73.9%	80	26.0%
Fosfomycin	238	97.9%	2	0.8%	274	96.1%	4	1.4%
Mecillinam	235	97.5%	3	1.2%	235	97.5%	3	1.2%
Nalidixic acid	220	90.5%	23	9.4%	251	90.6%	26	9.3%
Nitrofurantoin	232	95.4%	11	4.5%	272	86.3%	15	4.7%

Susceptibility strongly depends on the substance. In the ARES 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 investigation (Hummers-Pradier) of urine cultures from uncomplicated and complicated UTIs in female patients from general practices the resistance rate of *Escherichia coli* against amoxicillin, amoxicillin/clavulanic 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).

## 6. Antibiotic therapy

### 6.1. 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). Consensus 12/12.

The basic intention of antibiotic therapy is to rapidly relieve clinical symptoms (B-V). Consensus 11/12 (1 abstention).

In acute uncomplicated cystitis an antibiotic therapy should be recommended (B-Ib). Consensus 10/12 (2 abstentions, see minority vote of the DEGAM).

*Minority vote of the German Society for General and Family Medicine:*  
In acute uncomplicated cystitis symptomatic treatment by itself is a justifiable alternative to immediate antibiotic therapy (C-Ia).

In acute uncomplicated pyelonephritis an effective antibiotic therapy should be applied as soon as possible. (A-Ic). Consensus 12/12.

Asymptomatic bacteriuria increases the risk of infection in pregnant women and in patients with expected mucocutaneous traumatising interventions of the urinary tract. In these cases the patient should be screened for asymptomatic bacteriuria and treated if necessary (A-Ib). Consensus 12/12.

## 6.2. Preferred form of therapy

An oral antibiotic therapy should be the preferred method of treatment (**B-GCP**). Consensus 12/12.

For therapy of acute uncomplicated cystitis a short course therapy with an appropriate antibiotic should be possibly preferred (**B-Ia**). Consensus 12/12.

## 6.3. Choice of antibiotics

Selecting an antibiotic the following criteria have to be considered (Consensus 12/12):

- 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**). Consensus 12/12.

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**). Consensus 12/12.

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**). Consensus 12/12.

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**). Consensus 12/12.

## 6.4. Antibiotic therapy

### 6.4.1. Aminopenicillins ± Beta-lactamase inhibitors

Ampicillin, the better absorbable ampicillinesters and amoxicillin can no longer be recommended for empiric therapy because of the low / high susceptibility / resistance patterns (**A-IIa**). Consensus 12/12.

Aminopenicillins + betalactamase inhibitors are not the first choice for the empiric short course therapy of uncomplicated cystitis (A-Ib). Consensus 12/12.

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

#### 6.4.2. 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). Consensus 12/12.

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). Consensus 11/12 (1 abstention).

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). Consensus 11/12 (1 abstention).

#### 6.4.3. 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). Consensus 12/12.

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). Consensus 12/12.

#### 6.4.4. 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). Consensus 12/12.

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). Consensus 12/12.

Oral treatment with a single dose of fosfomycin trometamol is not indicated for the therapy of pyelonephritis or the treatment of men (A-V). Consensus 12/12.



#### **6.4.5. 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 (**lb**).

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-lb**). Consensus 10/12 (2 abstentions).

Nitrofurantoin was investigated in a short-term course of 3 days only against placebo. Prolonged treatment (5-7 days) showed better results (**A-IIb**).

#### **6.4.6. 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 (**lb**).

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 (**lb**).

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 K4) (**A-lb**). Consensus 12/12.

#### **6.4.7. Trimethoprim mono or in combination with a sulfonamide**

In the past cotrimoxazole (trimethoprim/sulfamethoxazole) and trimethoprim were the standard in empiric treatment of cystitis (**la**). Consensus 12/12.

Due to existing resistance rates, which according to the ARES 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 (**IIb**). 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**). Consensus 10/12 (2 abstentions, see minority vote of DEGAM).

*Minority vote of the German Society of General and Family Medicine:*

Despite higher resistance rates, the vast majority of patients are successfully treated with trimethoprim (**A-lb**).

## 7. Antibiotic therapy of acute uncomplicated UTI in special patient groups

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

#### 7.1.a. 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 expected within a few days and as no more consequences are drawn from the results of the urine culture (A-V). Consensus 12/12.

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). Consensus 12/12.

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-Ia). Consensus 12/12.

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 betalactamase-inhibitor should only be used alternatively in empiric treatment, if local resistance patterns (<20%) permit and first choice drugs cannot be used (B-V). Consensus 10/12 (2 abstentions, see minority vote of DEGAM).

**Minority vote of the German Society of General and Family Medicine:**  
Despite higher resistance rates, the vast majority of patients are successfully treated with trimethoprim (A-Ib).

Monitoring the efficacy of treatment of uncomplicated cystitis in otherwise healthy premenopausal women is unnecessary if they had become asymptomatic (B-V). Consensus 11/12 (1 abstention).

If therapy fails (within 2 weeks), non-compliance of patients, resistant pathogens or so far unrecognized risk factors should be considered. In these cases, differentiated instructions and a physical 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). Consensus 12/12.

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). Consensus 12/12.

**Table K4 Recommended short-term course for uncomplicated cystitis in otherwise healthy premenopausal women (without risk factors)**

Drug	Daily dosage	Duration
<b>Antibiotic of first choice (A)</b>		
Fosfomycin trometamol	3000mg qd	1 d
Nitrofurantoin	50mg q6h	7 d
Nitrofurantoin RT	100mg bid	5 d
Pivmecillinam*	200mg bid	7 d
Pivmecillinam*	400mg bid	3 d
<b>Antibiotic of second choice (B)</b>		
Ciprofloxacin	250mg bid	3 d
Ciprofloxacin RT	500mg qd	3 d
Levofloxacin	250mg qd	3 d
Norfloxacin	400mg bid	3 d
Ofloxacin	200mg bid	3 d
Cefpodoxime proxetil	100mg bid	3 d
<b>If local resistance patterns are known (<i>Escherichia coli</i> resistance rate &lt; 20%) (B)</b>		
Cotrimoxazole	160/800mg bid	3 d
Trimethoprim	200mg bid	5 d
RT= slow releasing form (= macrocrystalline form) *available in Austria and Scandinavia, not in Germany		

Consensus 10/12 (2 abstentions, see minority vote of DEGAM).

**Minority vote of the German Society of General and Family Medicine**  
Despite higher resistance rates, the vast majority of patients are successfully treated with trimethoprim (A-Ib).

#### 7.1.b. 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). Consensus 12/12.

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). Consensus 9/12 (3 abstentions).

Fluoroquinolones should be considered as first choice antibiotics if the local *Escherichia coli* resistance rate is <10% (B-Ib). Consensus 12/12.

Cefpodoxime proxetil should be considered in situations where other antibiotics e.g. fluoroquinolones cannot be applied (B-Ib). Consensus 12/12.

Cotrimoxazole should not be used anymore for empiric therapy of pyelonephritis (A-Ib) consensus 12/12. But Cotrimoxazole can be given as an oral sequence therapy after initial parenteral therapy, if pathogens are tested

susceptible for cotrimoxazole (C-Ib). Consensus 12/12. Trimethoprim has not been studied in this context.

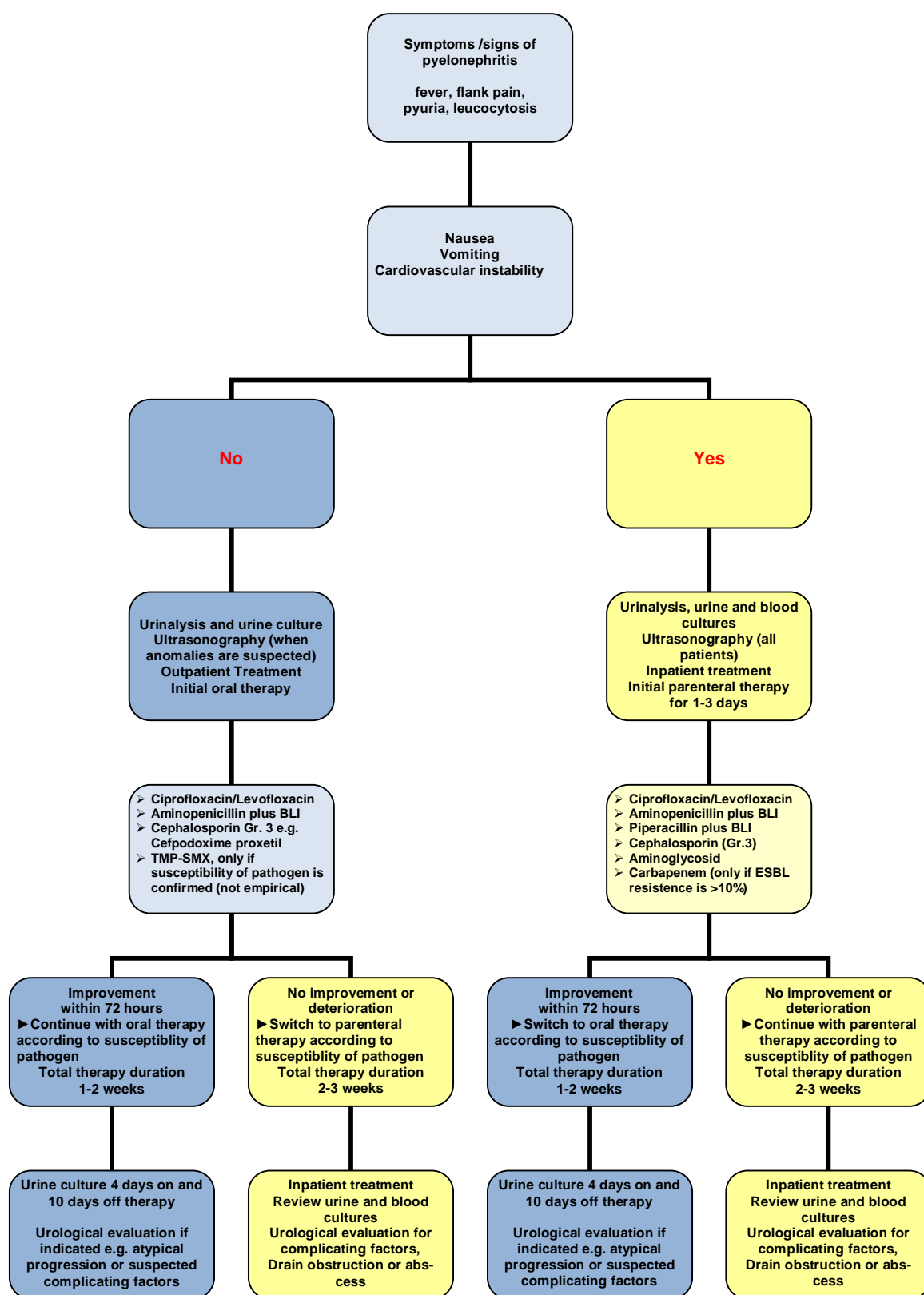
**Table K5 Recommended empiric antibiotic therapy of uncomplicated pyelonephritis in otherwise healthy premenopausal women (without risk factors)**

Oral therapy of mild to moderate cases		
Antibiotic of first choice (A) <sup>4</sup>	Daily dosage	Duration
Ciprofloxacin <sup>1</sup>	500-750mg bid	7-10 d
Ciprofloxacin RT	1000mg qd	7-10 d
Levofloxacin <sup>1</sup>	(250-) 500mg qd	7-10 d
Levofloxacin	750mg qd	5 d
Antibiotic of second choice (B)		
(similar clinical efficacy, microbiologically not equivalent with fluoroquinolones)		
Cefpodoxime proxetil	200mg bid	10 d
Ceftibuten	400mg qd	10 d
If susceptibility of pathogens is confirmed (B)		
(not for empiric therapy)		
Cotrimoxazole	160/800mg bid	14 d
Amoxicillin/Clavulanic acid <sup>2,3</sup>	0,875/0,125g bid	14 d
Amoxicillin/Clavulanic acid <sup>2,3</sup>	0,5/0,125g tid	14 d
<sup>1</sup> Low doses studied, high dosage recommended by experts		
<sup>2</sup> Not investigated in convincing clinical studies.		
<sup>3</sup> Primarily for Gram-positive pathogens		
<sup>4</sup> If <i>Escherichia coli</i> resistance is <10%		
Initial parenteral therapy of severe pyelonephritis		
After clinical improvement therapy can be switched to one of the above-mentioned oral therapy regimens if susceptibility of pathogens is confirmed. The total duration of therapy is 1-2 weeks, therefore duration of parenteral antibiotic therapy is not noted.		
Antibiotic of first choice (A) <sup>7</sup>	Daily dosage	
Ciprofloxacin	400mg bid	
Levofloxacin <sup>1</sup>	(250-) 500mg qd	
Levofloxacin	750mg qd	
Antibiotic of second choice (B)		
Cefepim <sup>1,4</sup>	1-2g bid	
Ceftazidim <sup>2</sup>	1-2g tid	
Ceftriaxon <sup>1,4</sup>	1-2g qd	
Cefotaxim <sup>2</sup>	2g tid	
Amoxicillin/Clavulanic acid <sup>2,3</sup>	1,0/0,2g tid	
Amoxicillin/Sulbactam <sup>2,3</sup>	1,0/0,5g tid	
Piperacillin/Tazobactam <sup>1,4</sup>	2,5-4,5g tid	
Amikacin <sup>2</sup>	15mg/kg qd	
Gentamicin <sup>2</sup>	5mg/kg qd	
Doripenem <sup>4,5</sup>	0,5g tid	
Ertapenem <sup>4,5</sup>	1g qd	
Imipenem/Cilastatin <sup>4,5</sup>	0,5/0,5g tid	
Meropenem <sup>4,5,6</sup>	1g tid	
<sup>1</sup> Low doses studied, high dosage recommended by experts		
<sup>2</sup> Not investigated in convincing clinical studies.		
<sup>3</sup> Primarily for Gram-positive pathogens		
<sup>4</sup> Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible)		
<sup>5</sup> Only if ESBL resistance > 10 % (ESBL - extended spectrum beta-lactamases)		
<sup>6</sup> Only high dosage studied		
<sup>7</sup> If <i>Escherichia coli</i> resistance <10%		

### 7.1.c. 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). Consensus 11/12 (1 abstention).

**Figure K2 Clinical management of acute pyelonephritis in female adult patients**



BLI = betalactamase inhibitor; TMP = Trimethoprim; SMX = Sulfamethoxazole

## **7.2. 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). Consensus 12/12.

Asymptomatic bacteriuria and symptomatic UTI in pregnancy have to be treated with antibiotics to avoid serious consequences for mother and child (A-Ia). Consensus 12/12.

### **7.2.a. 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). Consensus 12/12.

### **7.2.b. Acute uncomplicated pyelonephritis in otherwise healthy pregnant women without risk factors**

During pregnancy inpatient treatment of pyelonephritis has to be considered (A-V). Consensus 12/12.

For empiric treatment cephalosporins of group 2 and 3 are mainly recommended (B-V). Consensus 12/12.

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). Consensus 12/12.

### **7.2.c. 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). Consensus 12/12

## **7.3. Antibiotic therapy of acute uncomplicated UTI in otherwise healthy postmenopausal women**

### **7.3.a. 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). Consensus 12/12.

Selection and dosage of antibiotics comply with treatment regimens of premenopausal women (B-V). Consensus 12/12.

#### **7.3.b. 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 (B-V). Consensus 12/12.

#### **7.3.c. Asymptomatic bacteriuria in otherwise healthy postmenopausal women**

Asymptomatic bacteriuria in otherwise healthy postmenopausal women is apparently not associated with adverse outcomes. Therefore neither screening nor therapy are generally necessary (A-IIb). Consensus 11/12 (1 abstention).

### **7.4. Antibiotic therapy of acute UTI in otherwise healthy young men**

#### **7.4.a. Acute uncomplicated cystitis in otherwise healthy young men**

For the empiric oral therapy of acute uncomplicated cystitis in young men, the same antibiotics are recommended as in women (Table 4), with the exceptions of fosfomicin trometamol (single dose), pivmecillinam and nitrofurantoin (B-V). Consensus 12/12.

#### **7.4.b. Acute uncomplicated pyelonephritis in otherwise healthy young men**

For the empiric 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-Ib). Consensus 12/12.

Duration of therapy is usually 7-10 days (B-IIa). Consensus 12/12.

#### **7.4.c. 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). Consensus 9/12 (3 abstentions).

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

### **7.5.a. 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). Consensus 12/12.

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). Consensus 12/12.

In acute uncomplicated cystitis in patients with diabetes mellitus and stable glycaemic metabolism a short-term antimicrobial therapy is justified (C-V). Consensus 12/12.

In severe insulin resistance, threatening organ complications and a tendency to metabolic decompensation inpatient treatment should be considered (A-V). Consensus 12/12.

### **7.5.b. 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). Consensus 12/12.

### **7.5.c. Asymptomatic bacteriuria in otherwise healthy patients with diabetes mellitus and stable glycaemic metabolism**

In otherwise healthy patients with diabetes mellitus with stable glycaemic metabolism (HbA1c <7.5%, no predisposition to hypo- or hyperglycaemia, diabetic nephropathy) and without obstructive anatomical changes no antibiotic therapy is necessary (A-Ib). Consensus 11/12 (1 abstention).

## **7.6. Asymptomatic Bacteriuria**

Asymptomatic bacteriuria increases the risk of infection in pregnant women and in patients with expected mucocutaneous traumatising interventions of the urinary tract. In these cases patients should be screened for asymptomatic



bacteriuria and treated if necessary. Supporting studies are available for pregnancy and transurethral resection (A-Ib). Consensus 12/12.

Asymptomatic bacteriuria obviously has no adverse effects in the following groups of patients. Therefore neither screening nor treatment are recommended. Consensus 11/12 (1 abstention)

- premenopausal, non pregnant women (A-Ib)
- . diabetic women\* (A-Ib).
- . older persons living in the community (A-IIb)
- . elderly institutionalized subjects (A-Ib)
- patients with spinal cord injury (A-IIb)
- . catheterized patients while the catheter remains in situ (A-Ia).

\*this applies to diabetics with stable glycaemic metabolism.