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The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1

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Abstract
Objectives: We aimed to update the 2010 evidence- and consensus-based national clinical guideline on the diagnosis and management of uncomplicated urinary tract infections (UTIs) in adult patients. **Materials and Methods:** An interdisciplinary group consisting of 17 representatives of 12 medical societies and a patient representative was formed. Systematic literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library to identify literature published in 2010–2015. **Results:** We provide 75 recommendations and 68 statements in the updated evidence- and consensus-based national clinical guideline. The diagnostics part covers practical recommendations on cystitis and pyelonephritis for each defined patient group. Clinical examinations, as well as laboratory testing and microbiological pathogen assessment, are addressed. **Conclusion:** In accordance with the global antibiotic stewardship initiative and considering new insights in scientific research, we updated our German clinical UTI guideline to promote a responsible antibiotic use and to give clear hands-on recommendations for the diagnosis and management of UTIs in adults in Germany for healthcare providers and patients.

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Background

Uncomplicated, bacterial, community-acquired urinary tract infections (UTIs), including cystitis and pyelonephritis, are among the most common infections in the outpatient setting. Data on antibiotic consumption in uncomplicated UTIs from the German Barmer health insurance, one of the largest health insurance funds, on prescribing practice in the treatment of cystitis are in sharp contrast to the recommendations of the German clinical guideline on uncomplicated UTIs of 2010 [1] not to use fluoroquinolones in uncomplicated cystitis. In contrast to the guideline recommendations, primarily fluoroquinolones (48%) were prescribed [2].

Antibiotic resistance is a growing global problem that leads to significant challenges and costs in the health care system [1–5]. The resistance level of pathogens against commonly used antibiotics of uncomplicated UTIs has significantly increased in recent years. Recognition of this fact has led to an international re-evaluation of therapeutic recommendations in uncomplicated UTIs [4]. In accordance with this global initiative and the achievements in the antibiotic stewardship movement, we updated our German clinical UTI guideline to promote a responsible antibiotic use in the management of UTIs in adults in Germany.

The German Society for Urology (DGU) was heading the update process of the interdisciplinary Association of Scientific Medical Societies in Germany S3 guideline. Funding by the pharmaceutical industry was strictly avoided; the conflicts of interest by the members of the guideline group were disclosed and discussed openly. The German Association of Scientific Medical Societies in Germany (AWMF) S3 guideline is free for download available in a short and long version on the website of the AWMF (http://www.awmf.org/leitlinien/detail/ll/043–044.html) [6]. The category S3 refers to the German guideline classification form, where S3 represents the highest methodological standard and involves both evidence- and consensus-based concepts to achieve guideline recommendations from an interdisciplinary panel group [7].

The guideline recommendations address all medical specialties involved in the diagnostics, therapy, management, and prevention of acute uncomplicated UTIs (Table 1), for example, general practitioners, gynecologists, infectious disease specialists, microbiologists, nephrologists, urologists, and laboratory physicians.

Here, we present the main content of the updated guideline in 2 parts. Part I focuses on the recommendations regarding the definition of patient groups and the diagnostics of uncomplicated bacterial UTI acquired in the outpatient setting in adult patients. Part II will cover the treatment of acute episodes of cystitis and pyelonephritis and prophylaxis of recurrent UTIs.

Objective

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

Methods

The AWMF S3 clinical guideline is based on an interdisciplinary consensus group consisting of 17 representatives of 12 medical societies and a member of a patient organization, thus considering all relevant medical specialties involved in the diagnostics and the management of UTIs in adult patients (Table 1).

A systematic literature search was conducted in the databases MEDLINE, EMBASE, and the Cochrane Library to identify the literature published between January 2010 and December 2015. International clinical guidelines, systematic reviews, meta-analysis, and randomized clinical trials on this topic were considered for inclusion. For specific chapters, like epidemiology, collateral damage, or diabetic patients with UTI, individual searches were conducted and the experts selected specific literature outside the above-mentioned inclusion criteria. The literature searches identified 2,909 publications, which were screened for inclusion. Finally, 156 publications (primary and secondary studies as well as clinical guidelines) were considered as relevant. The risk of bias of the included studies was assessed using AGREE [8], AMSTAR [9], or the Cochrane tool for randomized clinical trials [10]. The Oxford criteria were used for the level of evidence ratings (Table 2) [11]. A formal consensus was achieved through the nominal group process under the guidance of an external moderator from the AWMF with the representatives of the participating medical associations. The evidence-based recommendations were developed in a consensus conference.

The following 3 grades of recommendations were categorized:
- A: strong recommendation: should/should not (German: "soll")
- B: recommendation: ought to/ought not to (German "sollte")
- C: open recommendation: may be considered

The process of development of the S3 Guideline is illustrated in Figure 1.

Definition of UTIs

A UTI is classified as uncomplicated if there are no relevant functional or anatomical anomalies in the urinary tract, no relevant renal functional impairment and

Table 1. Participating medical societies and working groups

Medical Society or working group	Participants in the update 2017
German Society of Urology (DGU, Deutsche Gesellschaft für Urologie) – lead organization	Dr. J. Kranz Prof. Dr. K.G. Naber Dr. S. Schmidt Dr. L. Schneidewind Priv. Doz. Dr. W. Vahlensieck Prof. Dr. F.M.E. Wagenlehner
German Society for General and Family Medicine (DEGAM, Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin)	Prof. Dr. E. Hummers Priv. Doz. Dr. G. Schiemann
German Society of Gynecology and Obstetrics (DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe)	Prof. Dr. U. Hoyme Dr. M. Kunze
German Society for Hygiene and Microbiologie (DGHM, Deutsche Gesellschaft für Hygiene und Mikrobiologie)	Dr. E. Kniehl
German Society of Infectious Diseases (DGI, Deutsche Gesellschaft für Infektiologie)	Dr. S. Helbig Dr. F. Mandraka
German Society of Nephrology (DGfN, Deutsche Gesellschaft für Nephrologie)	Prof. Dr. R. Fünfstück Prof. Dr. U. Sester
Paul Ehrlich Society for Chemotherapy (PEG, Paul-Ehrlich-Gesellschaft für Chemotherapie)	Prof. Dr. R. Fünfstück Dr. E. Kniehl Prof. Dr. K.G. Naber Prof. Dr. F.M.E. Wagenlehner
Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL)	Prof. Dr. W. Hofmann
Bundesverband Deutscher Krankenhausapotheker (AKDA)	Dr. C. Lebert
CA-Deutschland e.V., Förderverein Interstitielle Zystitis (patient representative)	B. Mündner-Hensen

Table 2. Level of evidence after Oxford 2009 classification system [11]

Level of evidence	Diagnostics	Therapy
Ia	Systematic review (SR; with homogeneity) of level 1 diagnostic studies; clinical decision rule with 1b studies from different clinical centres	SR (with homogeneity) of randomized controlled studies (RCT)
Ib	Validating cohort study with good reference standards, or clinical decision rule tested within 1 clinical centre	Individual RCT (with narrow confidence interval)
Ic	Absolute SpPins* and SnNouts*	All or none principle
IIa	SR (with homogeneity) of level >2 diagnostic studies	SR (with homogeneity) of cohort studies
IIb	Exploratory cohort study with good reference standards, clinical decision rule after derivation, or validated only on split-sample or databases	Individual cohort study (including low quality RCT)
IIc		Outcomes research, ecological studies
IIIa	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of case-control studies
IIIb	Non-consecutive study, or without consistently applied reference standards	Individual case-control study
IV	Case-control study, poor or non-independent reference standard	Case-series (and poor-quality cohort and case-control studies)
V	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles

* An "Absolute SpPin" is a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis [11].
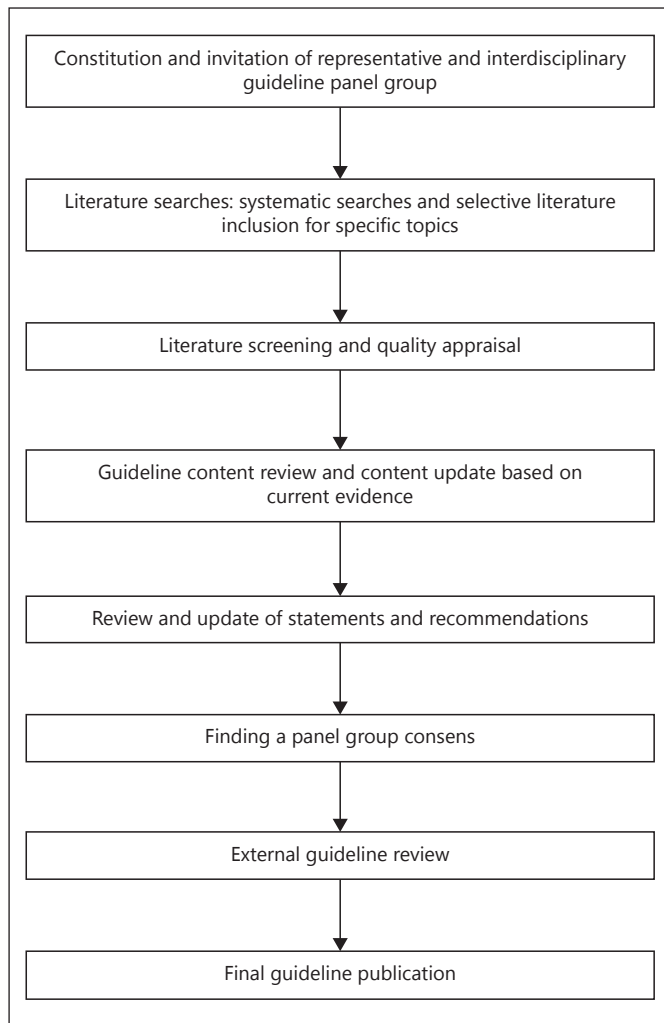
Fig. 1. Steps in the development of the guideline.

no relevant concomitant disease that would promote the UTI, or the risk of developing serious complications [3].

- Acute uncomplicated cystitis: A lower UTI (cystitis) is assumed when the acute symptoms refer only to the lower urinary tract, for example, urgency, pain on micturition (dysuria), pollakisuria, and pain above the symphysis.
- Acute uncomplicated pyelonephritis: An upper UTI (pyelonephritis) ought to be assumed if, in the case of acute symptoms, flank pain, pain on palpation of the flank, and/or fever (>38°C) persist.
- Asymptomatic bacteriuria: Clinically symptomatic UTI is distinguished from asymptomatic bacteriuria. The term 'asymptomatic UTI' ought not to be used.

- Recurrent uncomplicated UTIs: A recurrent UTI is assumed if relapse rates of ≥2 symptomatic episodes occur within 6 months or ≥3 symptomatic episodes within 12 months.

Definition of Patient Groups

The following patient groups with uncomplicated UTI ought to be distinguished for diagnostic and therapeutic purposes:
- Otherwise healthy, non-pregnant premenopausal women (reference group).
- Otherwise healthy pregnant women.
- Otherwise healthy postmenopausal women.
- Men with uncomplicated UTI.
- Patients with diabetes mellitus.

Diagnostics

Diagnostic methods are designed to detect the presence of UTIs, but also, when appropriate, to ascertain the etiology (bacterial spectrum) that triggered the infection and how it can be treated (susceptibility to antibiotics).

Clinical Examination
As type and frequency of anatomical or symptomatic complications may differ in individual patient groups, group-specific diagnostic strategies ought to be applied (V).

Women with suspected uncomplicated UTIs should be asked if they:
1. Have relevant pain on micturition and urgency
2. Suspect a UTI as a cause themselves
3. Have vaginal discomfort.

If the answer to question 1 and/or 2 is "yes," a UTI is very likely. For vaginal complaints, a differential diagnosis should also be considered (A, Ia).

Alternative diagnoses and gynecological examination ought to be considered in women who suffer from vaginal itching or vaginal discharge (B, Ia): the presence of pain on micturition, urgency, and occasional hematuria increases the likelihood of a UTI. If one or more of these symptoms are present, a positive dipstick (nitrite or leukocyte esterase alone or in combination) further increases the likelihood of a UTI (Ia). Diagnosis without direct patient contact is possible and has been successfully evaluated in some studies on telephone management or using an interactive computer response system. While this approach proved to be feasible in terms of patient satisfaction and cure rates,

most of the studies used a retrospective design and did not assess diagnostic accuracy. The value of a non-personal doctor-patient treatment (telemedicine) has not been investigated in Germany. Experiences with telemedicine from other countries cannot directly be transferred to the German healthcare system (Ib).

Diagnostics in Different Patient Groups

In the following, specific recommendations for the diagnosis in non-pregnant premenopausal women without other relevant concomitant diseases are presented (standard group). For the other patient groups, the specific recommendations on diagnosis are listed in the guideline document (http://www.awmf.org/leitlinien/detail/ll/043-044.html).

Diagnosis of Acute Uncomplicated Cystitis in Non-Pregnant Premenopausal Women

If women who have no risk factors for complicated UTIs complain of typical symptoms (pain on micturition, pollakisuria, urgency), have no vaginal symptoms (itching, altered discharge), have no fever and no flank pain, the presence of an uncomplicated cystitis may be considered with high probability (IIa).

In the first manifestation of an acute UTI or, if the patient is unknown to the doctor, a symptom-related medical examination with clinical examination ought to be performed (B, V). The diagnosis of uncomplicated cystitis based on clinical criteria may be considered with high probability (sensitivity of 94.7%, specificity of 82.4%) with the use of the validated questionnaire (Acute Cystitis Symptom Score [ACSS]) [12], which assesses the severity of the symptoms and the course of the disease (IIb). The validated questionnaire ACSS may be considered to follow the course of cystitis over time and the effect of therapy (IIb) [13]. The ACSS questionnaire is translated and validated in several languages (www.acss.world).

In women with uncomplicated, non-recurrent or -refractory cystitis, with clear clinical symptoms, no microbiological examination is recommended (IIIc). In symptomatic women, the detection of *Escherichia coli* in the midstream urine, independent of the number of pathogens, is predictive for a bacterial UTI. In contrast, the detection of Enterococci and group B Streptococci in the midstream urine is not predictive for a UTI (Ib).

Diagnosis of Uncomplicated Acute Pyelonephritis in Non-Pregnant Premenopausal Women

In the diagnosis of uncomplicated acute pyelonephritis in non-pregnant women without other relevant concomitant diseases, the clinical examination follows the general principles (see above). In addition, a physical examination and urine examination including a urine culture should be carried out (A, V). In the diagnosis of uncomplicated acute pyelonephritis in non-pregnant women without other relevant concomitant diseases, further examinations (e.g., sonography) should be performed to exclude complicated factors (A, V).

Diagnosis of Asymptomatic Bacteriuria in Non-Pregnant Premenopausal Women

In non-pregnant women without other relevant concomitant diseases, screening for asymptomatic bacteriuria ought not to be carried out (A, Ia).

Diagnosis of Persistent and Recurrent UTIs in Non-Pregnant Premenopausal Women

In patients with persistent hematuria or persistent detection of pathogens other than *E. coli*, further studies such as urethrocystoscopy and further imaging ought to be performed (B, V). In patients with recurrent UTIs, a urine culture and a single sonography ought to be performed. Further invasive diagnostics ought not to be performed (B, Ib).

Urine Diagnostic Procedures

The gold standard for the diagnosis of UTI is the urine examination, including quantitative urine culture and its assessment, with appropriate clinical examinations and typical symptom assessment (V).

Urine Dipsticks

In patients with a low pretest probability, a negative test for nitrite/leukocytes may be considered to rule out UTI with sufficient certainty (IIa). The detection of blood, leukocytes, and nitrite independently increases the likelihood of the presence of a UTI. The combination of the positive findings further increases the likelihood of the diagnosis (Ib).

Urine Microscopy

With urine microscopy, it may be considered that UTIs can be largely ruled out, if the investigator has adequate experience (Ia). The centrifugation of the urine for the microscopic detection of bacteria does not lead to a greater accuracy of the diagnosis (Ib). It may be considered, that if leukocytes are missing at urine microscopy, a UTI can be excluded (IIIb).

Table 3. Cut-off values (colony forming units [CFU]/mL) for the diagnosis of different urinary tract infections and asymptomatic bacteriuria [15]

Diagnosis	Evidence of bacteria, CFU/mL	Urine collection
Acute uncomplicated cystitis in women	10^3	Midstream urine
Acute uncomplicated pyelonephritis	10^4	Midstream urine
Asymptomatic bacteria	10^5	In women: evidence in 2 consecutively midstream urine samples. In men: evidence in 1 midstream urine sample. For catheter urine: 10^2 CFU/mL

Urine Culture

In patients with typical symptoms, colony counts of up to 10.3–10.4 CFU/mL of typical uropathogens can already be clinically relevant for clinical symptoms (Table 3) if they were detected in mono cultures (i.e., only one type of bacteria) of typical uropathogens (V).

Urine samples for cultural microbiological diagnostics need to be processed immediately. If the sample cannot be processed immediately, the urine needs to be stored at 2°–8°C until further examination (V). Quantitative urine culture with species identification and susceptibility testing is an indispensable prerequisite for targeted therapy, especially in pyelonephritis and recurrent UTIs (V).

Flow Cytometry

Urine flow cytometry is a laboratory-based method to standardize urine sediment analysis. The automated analyzers are capable to quantify for examples white blood counts (WBC) or bacteria. While clinical performance with a sensitivity (specificity) of 0.87 (0.67) for WBCs and 0.92 (0.60) for bacteria seems promising, a systematic review and meta-analysis concluded that due to methodological shortcomings further studies are needed [14].

Imaging Diagnostics and Endoscopy

For the diagnosis of acute pyelonephritis in healthy women without complicating factors, further diagnostic procedures are recommended to rule out complicating factors (e.g., sonography; V). In women without recurrent UTI and without relevant comorbidities, routine cystoscopy ought not to be performed (B, IIb).

Differential Diagnosis – Diagnostic Strategies

In the case of non-specific symptoms, or inconsistent urine examination, including negative urine culture, other diagnoses, such as gynecological infections, like chlamydia or trichomonas infection, should be considered at an early stage (V).

Bacterial Spectrum

The most common cause of uncomplicated UTIs is *E. coli*, followed by *Staphylococcus saprophyticus*, *Klebsiella pneumoniae,* and *Proteus mirabilis*. Other pathogens are rare (Ia). *Enterococci* are most commonly found in mixed infections. Therefore, their pathogenicity is uncertain in uncomplicated UTIs (Ic).

Figure 2 shows the clinical microbiological pathway for diagnosis and therapy of symptomatic patients.

Key Messages

Uncomplicated UTIs are responsible for a large proportion of all antibiotic prescriptions and pathogen resistance is increasing worldwide. This is a major challenge in health care and therefore requires a responsible and restricted handling of antibiotic prescriptions across all health care professions.

Patient-reported symptom assessment is a key in the diagnostic evaluation of acute cystitis. The validated ACSS is an accurate tool for the diagnosis of acute uncomplicated cystitis in women. It may be considered in the patient follow-up for clinical outcome assessment and in the determination of the effect of therapy.

The performance of a differential diagnosis is important in cases of non-specific symptoms, or inconsistent urine examination, including negative urine culture, and other diagnoses, such as gynecological infections with chlamydia or trichomonas, should be considered at an early stage of patient examination.

The most common cause of uncomplicated UTIs is *E. coli*, followed by *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. Other pathogens are rare. Urine analysis, including microbiology, is the gold
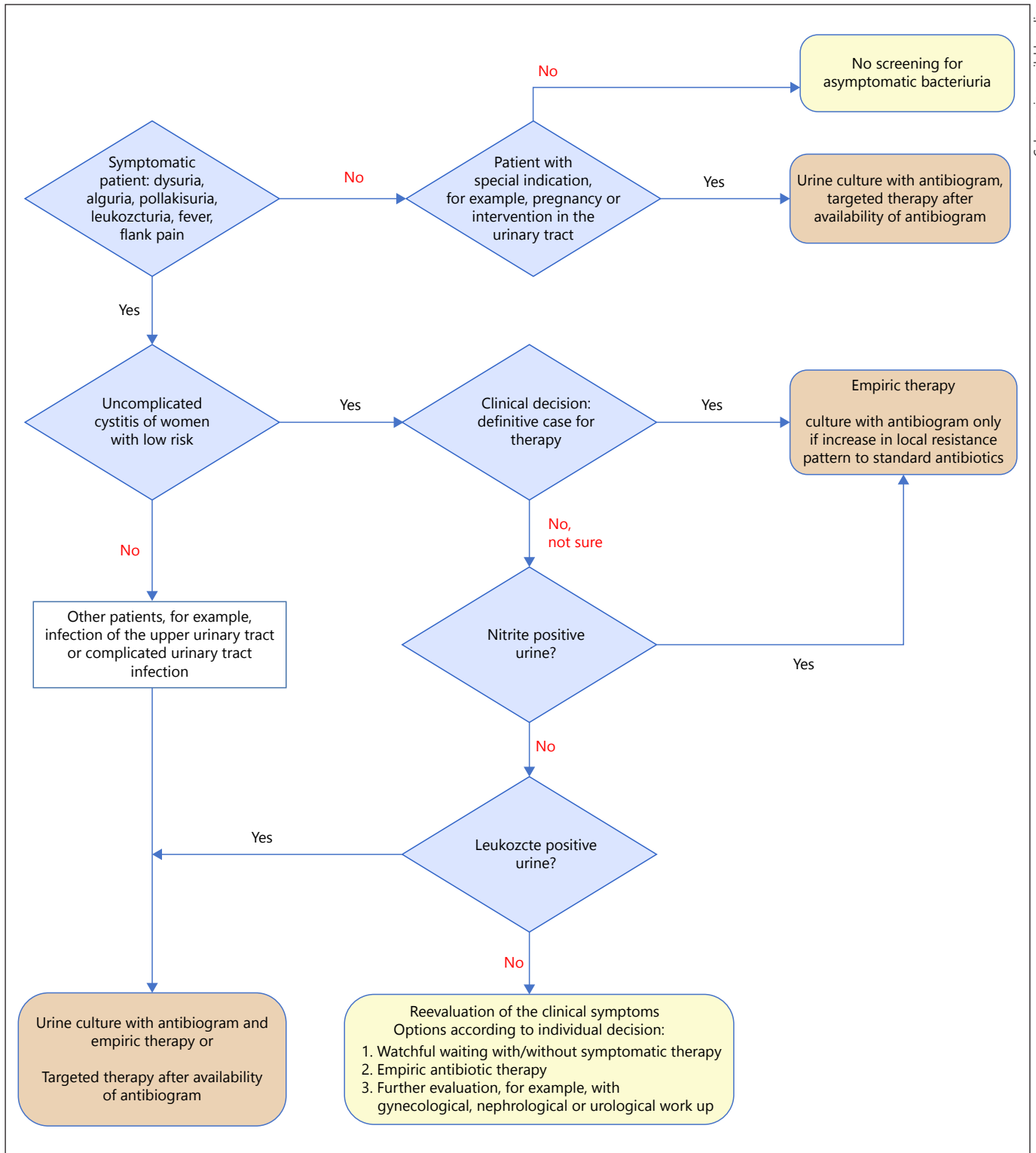
Fig. 2. Clinical microbiological pathway for diagnosis and therapy of symptomatic patients. Adapted from the guideline version [6].

standard for the diagnosis of UTI, including quantitative urine culture, with appropriate clinical examinations and typical symptom assessment. Nevertheless, performing urine culture in every patient is economically not feasible; therefore, in women who have no risk factors for complicated UTIs, complain of typical symptoms (e.g., pain on micturition, frequent urination, urgency), have no vaginal symptoms (itching, altered discharge), have no fever, and no flank pain, the presence of an uncomplicated cystitis may be considered with high probability.

In patients with persistent hematuria or persistent detection of pathogens other than *E. coli*, further studies such as urethrocystoscopy and further imaging ought to be performed. In patients with recurrent UTIs, a urine culture and a single sonography should be performed.

Disclosure Statement

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