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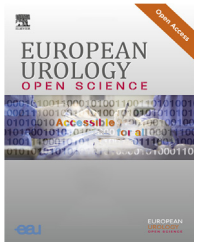

European Association of Urology

Infections

The Importance of Antimicrobial Strategies Associated with Clinical Cure and Increased Microbiological Eradication in Patients with Complicated Urinary Tract Infections and High Risk of Relapse

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Abstract

Background and objective: Complicated urinary tract infections (cUTIs) are serious, potentially life-threatening infections that occur in patients with an increased disease progression risk. Antimicrobial resistance represents an important health issue worldwide, contributing to relapses, which can generate further resistances. It is necessary to clarify the role of microbiological eradication as an additional objective in the management of cUTIs. Some publications suggest that relapses relate to insufficient bacterial suppression in the urinary tract. This study focuses on generating a consensus on how patients with cUTIs would benefit from effective antimicrobial agents associated with higher rates of bacterial eradication.
Methods: The nominal group technique was followed: systematic literature review, development of a questionnaire, expert panel meeting to discuss results, individual review of draft consensus document, and expert panel meeting to discuss final views and finalise the consensus document.
Key findings and limitations: Experts identified risk factors for cUTIs (patients with a higher risk of relapse, physiological obstruction of urinary tract, immune suppression, and previous relapse), and patients who would benefit most from a therapeutic strategy combining clinical cure and aim for microbiological eradication. While experts agreed that the scientific evidence discourages repetition of urine cultures after treatment, they proposed recommendations to prioritise antibiotics with higher evidence of microbiological eradication and close follow-up in patients with

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a higher risk of relapse, considering any symptoms appearing following clinical cure of the cUTI.

Conclusions and clinical implications: Selection of active antimicrobial agents associated with increased microbiological eradication should be prioritised in patients with cUTIs and a high risk of relapse.

Patient summary: Complicated urinary tract infections (cUTIs) occur in patients with an increased risk of disease progression or are caused by multidrug-resistant uropathogens. Antimicrobial resistance is of concern as it can result in relapses. Antimicrobial therapeutic strategies associated with increased microbiological eradication in cUTI patients with a high risk of relapse are crucial to prevent relapses and development of antibiotic resistance.

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections, and their aetiology is modified by factors such as age, gender, presence of diabetes, renal status, or urinary catheterisation [1–3]. Among UTIs, complicated urinary tract infections (cUTIs) are serious, potentially life-threatening infections that occur in patients with an increased risk of disease progression (eg, all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract) or are caused by multidrug-resistant uropathogens [4,5]. Antimicrobial resistance represents an important health issue raising concerns across the world, including publications from the World Health Organisation's "Global Action Plan on Antimicrobial Resistance" [6] and more recently by the council of the European Union's "Recommendations to fight against antimicrobial resistance" in 2023 [7]. Antibiotic resistance can result in relapses, which can, in turn, generate further resistances due to repeat antibiotic exposure to the causing bacteria. This cycle affects patients negatively, since it hinders the management of infections [8–10].

Both US Food and Drug Administration and European Medicines Agency (EMA) guidelines [11,12] recommend that any antimicrobial agent undergoing clinical trial evaluation for these types of infections demonstrate superiority based on the composite outcome of clinical and microbiological responses, assessed after finishing the therapy course (ie, post-therapy test of cure [TOC]) [11]:

1. Clinical success is evaluated based on resolution or marked improvement of symptoms.
2. Microbiological success is based on the decrease in the density of the original pathogen found at baseline from a previous urine culture (below $<10^3$ CFU).
3. The composite endpoint requires both clinical and microbiological success.

The eradicator performance of a treatment depends on several aspects, but particularly on the antimicrobial agents used, though this parameter is commonly considered only in clinical trials and not in the real life clinical scenario once the antibiotic is approved. Moreover, beyond clinical trial evaluations, it has been demonstrated that performing repeated urine cultures leads to inadequate antimicrobial treatments [13]. However, recently, Kadry *et al.* [14] conducted an analysis of data from 4852 patients participating in 13 phase 3 clinical trials in cUTIs, reporting that 18.0% of patients achieved clinical cure but with microbiological persistence and that they had a 5.5 times higher risk of relapse than patients presenting both clinical cure and microbiological eradication. During this trial, a lack of microbiological eradication in the TOC appeared to predict the likelihood of clinical relapse at subsequent visits, a very common problem in cUTIs and an incremental burden associated with symptom recurrence, the need for repeat clinical treatment, and hospital readmissions [14].

This landscape justifies the elaboration of a consensus document to translate the most recent scientific evidence to practical recommendations to be considered in clinical practice from the perspective of key stakeholders involved in managing cUTI patients in Spain. This consensus is aimed at defining the group of patients that would benefit more from antibiotic treatments that are associated with improved clinical outcomes but also with enhanced bacterial suppression.

2. Methods

The project was designed following the nominal group technique (NGT) methodology steps: (1) performance of a systematic literature review and synthesis of findings from which a questionnaire with key questions to experts was generated; (2) introduction of the NGT to the panel; (3) individual completion of the questionnaire by each expert, identifying and contributing own ideas to the topic; (4) first expert panel meeting to present and discuss results from answers to the questionnaire, and propose scope and outline of the consensus document; (5) individual review of draft consensus document; and (6) second expert panel meeting to discuss final views and finalise the consensus document.

2.1. Literature review and questionnaire development

A literature review was conducted in March 2024 to identify and synthesise relevant evidence available for the following topics: definitions and key concepts related to

cUTIs, antibiotic resistance in cUTIs in Spain, management of cUTIs in Spain, correlation between clinical cure, microbiological eradication, and relapse.

Search was performed under the scope of the Spanish National Health System, focusing on documents in Spanish and English, using scientific biomedical databases (PubMed, Medline, and Cochrane) complemented with grey literature sources (eg, Google scholar, EMA, clinical practice guidelines/protocols, and national and regional plans or strategies). Selection of publications for data extraction was based on titles and abstracts and finally full-text articles. Retrieved information was used to develop the questionnaire (see Supplementary material).

2.2. Expert panel

The study was conducted by a multidisciplinary panel of 6 experts, representing clinical specialities involved in management of cUTI patients in Spain: urology, infectious diseases, clinical microbiology, intensive care, preventive medicine, and hospital pharmacy.

2.3. Questionnaire completion and discussion sessions

The questionnaire was individually completed by each expert. Results were reconciliated and analysed. A consensus threshold was established at 5/6 participants (83%). Two online discussion sessions with the expert panel were performed to present results, discuss items for which consensus was not reached, and agree on the scope of the consensus document.

3. Results

3.1. Definitions

Differences in key definitions obtained from the literature review were reported by the experts. Some guidelines and protocols include different criteria when defining concepts such as cUTIs, relapse, or microbiological eradication, among other [3,15–18].

For the purposes of clarifying the scope and practical recommendations of this consensus, this section aims to establish the definitions agreed by the expert panel for each key concept. As detailed in Table 1, these definitions are to be used in the context of this consensus document and do not pretend to replace others established in clinical guidelines or consensus documents available from scientific societies.

3.2. Risk factors for cUTIs

The definition of cUTIs agreed in this study includes risk factors to be present in the patient as well as severe clinical symptomatology and/or systemic involvement (Table 2). Several risk factors for a UTI to be classified as a cUTI were identified in the literature [3,17,19–21].

Based on the evidence obtained in the literature review and the expert opinion of the panel, it was agreed on that the following risk factors for cUTIs should be considered for this study [2]:

Table 1 – Definitions related to cUTIs and antibiotic resistance

Term	Definition
cUTI	Urinary infection that occurs in an individual in whom it is considered that, because of host-associated risk factors, severe clinical symptomatology, and/or systemic involvement [2], it results in an infection that will be more difficult to resolve than an uncomplicated infection in the same person [2,17].
Clinical cure	Complete resolution of symptoms and signs of infection present at the time of diagnosis [12,31].
Microbiological eradication	Microbiological outcome, after antimicrobial treatment of a UTI, when the responsible uropathogen identified in the diagnostic urine culture is found at a concentration of $<1 \times 10^3$ CFU/ml in a urine culture obtained at the follow-up visit. In an RCT setting, it is considered necessary to wait for 7–14 d after the end of treatment to make this determination [12,31].
Relapse	The cUTI originated by the same microorganism as the initial infection with reappearance of the bacteriuria, within 2 wk following the end of the treatment of the initial infection [22,35].

CFU = colony forming unit; cUTI = complicated urinary tract infection; RCT = randomised controlled trial; UTI = urinary tract infection.

Table 2 – Risk factors for cUTIs agreed by the expert panel

Risk factors for cUTIs	
1. Obstruction at any point in the urinary tract	2. Immunosuppression
3. Presence of a foreign body in the urinary tract	4. Elevated postvoiding residue
5. Vesicourethral reflux	6. Diabetes mellitus poorly controlled or with target organ involvement
7. Recent instrumentation history	8. Recurrent UTIs (2 episodes in 6 mo or 3 in 1 yr)
9. UTI in Pregnant Women	10. Loss of anatomical integrity of the urinary tract
11. Isolation of multidrug-resistant micro-organisms	12. Critically ill patients admitted to the intensive care unit

cUTI = complicated urinary tract infection; UTI = urinary tract infection.

1. Experts considered that the presence of foreign objects, as well as alterations in the urinary tract are a relevant risk factor affecting the normal urinary flux and potentially creating reservoirs of bacteria, which can make the management of these patients difficult.
2. Certain patient profiles were identified to also have a higher risk of cUTIs due to their health status or comorbidities. Immunosuppressed patients are a clear group identified in the literature that present a higher risk of cUTIs, as well as pregnant women with UTIs, critically ill patients admitted to the intensive care unit, or patients with poorly controlled diabetes mellitus or with affectation of the target organ.
3. Finally, experts considered whether the UTI is originated by a multidrug-resistant bacterium, including extended spectrum β-lactamase producing bacteria; recurrent UTIs (two episodes in the last 6 mo or three in the last year) may also generate a cUTI due to potential management complications.

3.3. Complicated UTI patients with higher risk of relapse

The expert panel identified specific cUTI patient groups with a higher risk of relapse according to the literature (Table 3) [3,5,10,22].

Risk factors for relapse identified by the experts [3] were reasoned as follows:

1. The physiological obstruction at any point of the urinary tract, presence of a foreign object (including permanent catheters or stents), and patients with elevated postvoiding residue or the presence of bacterial reservoirs were identified as risk factors due to potential presence of reservoirs that could lead to relapse once clinical cure is achieved.
2. Immunosuppressed patients (ie, patients with human immunodeficiency virus, oncohaematological patients, and patients under treatment with biological drugs and corticosteroids) were also identified as a group of patients with a higher risk of relapse.
3. Finally, patients who had previously experienced a relapse were considered to have an increased risk of further relapses.

3.4. Complicated UTI patients who would benefit the most from microbiological eradication

Finally, after identifying patients with cUTIs according to the agreed definition for this work and the subgroups with a higher risk of relapse, the experts proposed that these groups of patients would benefit most from treatments that combine clinical cure with microbiological eradication (Table 4). Patient groups proposed are not exclusive and clinical criteria should always prevail and drive decision-making [3,15].

The recommendations are as follows:

1. Antibiotics with higher, demonstrated microbiological eradication results should be prioritised for treatment during the acute infection state in patients identified as those who would benefit most from microbiological eradication.
2. This prioritisation should be in accordance with antibiotic selection guidelines: target organism should be susceptible to the antibiotic, and the latter should exhibit the narrowest spectrum of therapeutic coverage according to the indication and patient characteristics [3,13,23].
3. A close follow-up should be performed afterwards, considering any clinical symptoms that may appear following clinical cure of the cUTI.

3.5. Proposed decision tree

A decision tree has been designed to aid decision-making and contribute to include the agreed recommendations in clinical practice (Fig. 1). The decision tree starts with the identification of patients with cUTIs and, within this group, those with an increased relapse risk:

1. If the patient presents an increased risk of relapse and was identified as a patient who would benefit from microbiological eradication, the therapeutic objective should include achievement of clinical cure and microbiological eradication. A close follow-up of the patient after resolution of the infection process should be performed.
2. Patients without increased risk of relapse or patients presenting an increased risk of relapse but not included in the groups of patients who would benefit most from microbiological eradication should be managed as indicated in current clinical guidelines, setting clinical cure as the therapeutic objective without any special consideration after resolution of the infection process.

4. Discussion

The increased antibiotic resistance in infections such as cUTIs, observed in the last years, is an important concern for administrations and health organisations throughout Europe [7,24]. Several regulations and guidelines have been developed to address the increasing rates of resistances observed. Despite the efforts, antibiotic resistance keeps increasing every year. One identified risk factor for the development of antibiotic resistance is infection relapse, on which new evidence has been published recently [15,25,26].

The consensus here presented aimed to consider new perspectives dealing with the management of cUTIs, introducing the concept of "patients with a high risk" of relapse. These patients would benefit from antimicrobial treatments that are associated with increased bacterial eradication, in order reduce the potential reappearance of cUTI symptoms once a first episode had been treated successfully. It is important to contextualise the new evidence generated

Table 3 – Complicated UTI patients with higher relapse risk agreed by the expert panel

cUTI patients with higher relapse risk
1. Obstruction at any point in the urinary tract
2. Presence of a foreign body in the urinary tract, including permanent urinary-vesical catheters or stents
3. Presence of percutaneous nephrostomy
4. Patients with cUTIs who have suffered a relapse
5. Elevated postvoiding residue
6. All immunosuppressed patients (eg, HIV, oncohaematology, patients on treatment with biologics or corticosteroids)
7. Hidden bacterial sites

cUTI = complicated urinary tract infection; HIV = human immunodeficiency virus; UTI = urinary tract infection.

Table 4 – Groups of cUTI patients who would benefit most from antimicrobial treatments associated with higher microbiological eradication agreed by the expert panel

Groups of cUTI patients who would benefit from microbial eradication
1. All immunosuppressed patients (eg, HIV, oncohaematology, patients on treatment with biologics or corticosteroids)
2. UTIs in pregnant women
3. Patients undergoing urological tract manipulations
4. Patient with previous infection and presence of a foreign body in the urinary tract who returns to consultation
5. Diabetes mellitus controlled poorly or with target organ involvement

cUTI = complicated urinary tract infection; HIV = human immunodeficiency virus; UTI = urinary tract infection.

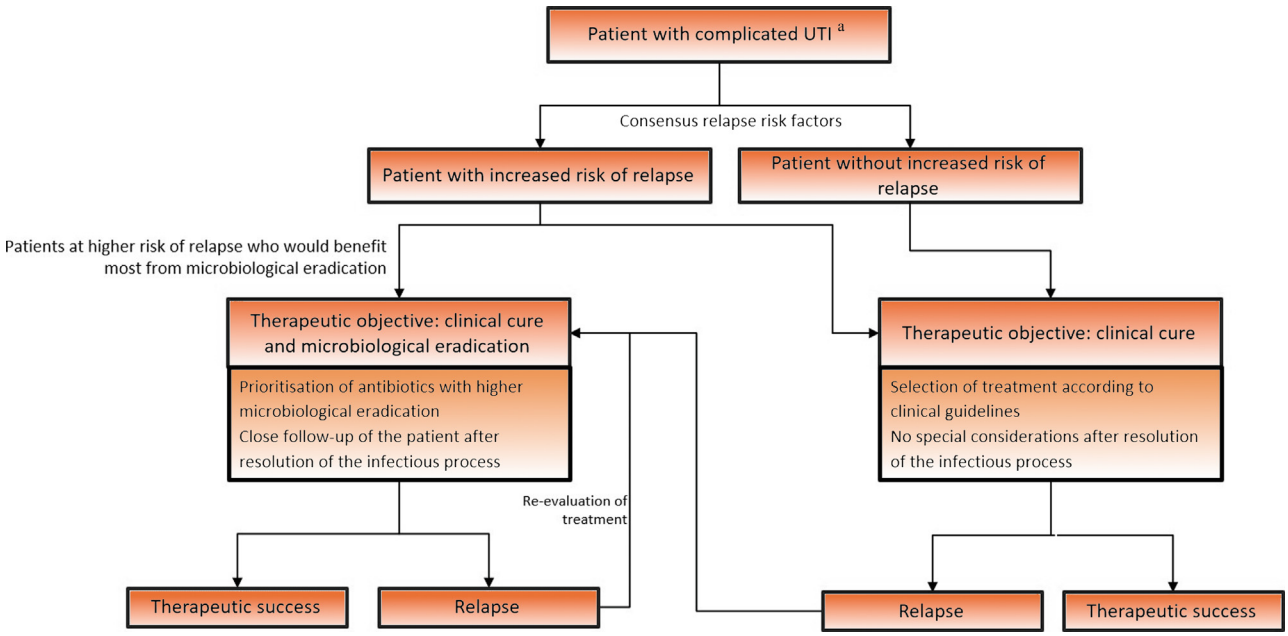

Fig. 1 – Proposed decision tree to establish microbiological eradication as a therapeutic objective. cUTI = complicated urinary tract infection; UTI = urinary tract infection. [a] For this consensus, cUTI is defined according to: consensus cUTI risk factors and severe clinical symptomatology and/or systemic involvement.

within the recommendations issued by the health authorities at national and European levels [7,13,27–30]. In Spain, the National Plan for Antibiotic Resistance (PRAN) [13] provides guidance to minimise the development of antibiotic resistance. For instance, it is not recommended to perform a urine culture in an asymptomatic patient due to cost and efficiency, and among all, to not treat asymptomatic bacteriuria, exposing patients to unnecessary antibiotics and increasing the risk of antimicrobial resistance.

Relapse is identified in the literature as a relevant risk factor for the development of resistances [3,31]. Patients with cUTIs that relapse can present an increased risk of complications and difficulties in clinical management [22]. Hence, patients with relapse risk factors would potentially benefit from microbiological eradication. The new, recently published evidence provided by Kadry *et al.* [14] on the relationship between a lack of microbiological eradication and relapses in cUTI patients raises new considerations in the management of these patients and the importance of determining certain groups of cUTI patients who would benefit from antimicrobial therapies with a high antimicrobial eradication profile, potentially decreasing the risk of relapses, readmissions, complications, and the development of additional antibiotic resistances.

National and international guidelines do not recommend the performance of urine cultures in an asymptomatic patient [13,16,23]. In accordance, this consensus also discourages the performance of urine cultures to confirm microbiological eradication but tries to define a new profile of patients who would benefit from specific antibiotic treatments with a favourable profile in terms of bacterial suppression. Despite this, the evidence suggests that achievement of eradication would reduce the relapse risk, as stated previously [32–34]. The experts agreed that patients with cUTIs and a higher risk of relapse would benefit from antibiotic treatments associated with high concentrations in the urinary tract and a good profile of bacterial suppression. This study is not exempt of limitations. First,

consider the eradicatory profile of a new antimicrobial agent for the management of cUTIs with a high risk of relapse. However, this evidence is based on evidence from clinical trials and should be investigated further in real clinical practice. In Spain, working groups in hospitals and primary care in the context of the PRAN and the antimicrobial stewardship programmes (in Spanish, "Programas de Optimización de Antimicrobianos") issue recommendations for best practices in the use of antibiotics, microbiology, and resistance profile mapping among other important activities. The results and recommendations included in this consensus document should be discussed with these groups to translate its recommendations into clinical practice routines, to improve cUTI patient care. Secondly, this study has included single experts from multidisciplinary specialities and scientific societies involved in the management of cUTI patients. Further discussion, and development of recommendations and consensus reached in this study should be performed by a larger group of experts, to contribute to test the scientific evidence that prompted this study and translate it into clinical practice. Finally, the proposed decision tree should also be also tested to evaluate its adequacy in clinical practice, as well as the measurement of its impact, continuously evaluating the impact of any intervention to propose potential improvements or modifications.

5. Conclusions

This study represents the first approach to translate the scientific evidence to define a profile of patients with cUTIs and a high risk of relapse, who would benefit from effective antimicrobial strategies associated with higher rates of microbial eradication, besides clinical cure, in cUTIs, into clinical practice. The consensus document has received the scientific endorsement from the following scientific societies: Spanish Society of Urology (AEU), Spanish Society of Infectious Disease and Clinical Microbiology (SEIMC), Spanish Society of Preventive Medicine, Public Health and Healthcare Management (SEMPSPGS) and the Spanish Society of Hospital Pharmacy (SEFH). The recommendations made in this study should be discussed further and analysed to grant best practices and improve health care.

***Author contributions*:** Alicia Gil had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gil.
Acquisition of data: Medina Polo, Alfonso Sánchez, Arca-Suárez, Estella, Membrillo de Novales, Periañez Párraga.
Analysis and interpretation of data: Medina Polo, Alfonso Sánchez, Arca-Suárez, Estella, Membrillo de Novales, Periañez Párraga, Gil, González, Blasco.
Drafting of the manuscript: Blasco, Gil.
Critical revision of the manuscript for important intellectual content: Medina Polo, Alfonso Sánchez, Arca-Suárez, Estella, Membrillo de Novales, Periañez Párraga.
Statistical analysis: González.
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Appendix A. Supplementary material

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