Adherence to European Association of Urology Guidelines and State of the Art of Glycosaminoglycan Therapy for the Management of Urinary Tract Infections: A Narrative Review and Expert Meeting Report

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\textbf{Abstract}

\textbf{Context:} Urinary tract infections (UTIs) have a significant impact on patient’s quality of life and society. Antibiotic therapy is the primary approach for the management of UTIs; however, it has major limits in the prevention of recurrent UTIs (rUTIs), also increasing the risk of development of multidrug-resistant microorganisms.

\textbf{Objective:} The aim of this paper is to discuss the European Association of Urology guidelines for the management of UTIs/rUTIs, the level of adherence to these recommendations, and the available evidence on the use of glycosaminoglycans (GAGs) as a possible alternative treatment to prevent rUTIs.

\textbf{Evidence acquisition:} This narrative review and expert meeting report is based on a literature search concerning the currently available UTI guidelines, the results of a survey administered to 227 urologists, and the opinion of an expert panel in the field of UTIs.

\textbf{Evidence synthesis:} Results obtained from the literature search showed that adherence to guidelines is not optimal. The survey demonstrated that antibiotics remain one of the treatments of UTIs. However, most of the urologists are aware of the problem caused by the resistance to antibiotics and prefer alternative methods for the prophylaxis of UTIs. Considering the alternative methods, the authors concluded that GAG therapy is highly effective in preventing rUTIs.

\textbf{Conclusions:} Adherence to the international guidelines is important to align the clinical practice and avoid the spreading of antibiotic resistance. The survey outlines that the misuse and overuse of antibiotics are major problems; an analysis of clinical evidence confirms that GAG therapy is a valuable therapeutic approach to prevent the recurrence of episodes of UTIs and to limit the onset of antibiotic resistance.

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1. Introduction

Urinary tract infections (UTIs) are bacterial infections of the bladder and associated structures [1]. Clinically, UTIs are classified as uncomplicated or complicated. Uncomplicated UTIs, differentiated into lower (cystitis) and upper (pyelonephritis) UTIs, usually affect healthy individuals without structural or neurological urinary tract abnormalities. The most common risk factors are sexual intercourse, spermicide use, having a new sex partner, having a mother with a history of UTIs, having had UTIs during childhood, and asymptomatic bacteriuria treatment [2]. Women are most affected due to the position of the urethra, favoring easier bacterial colonization. Complicated UTIs are associated with factors such as urinary obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy, and the presence of foreign bodies such as calculi, catheters, or other drainage devices. Uncomplicated and complicated UTIs are most frequently caused by uropathogenic Escherichia coli [3].

UTIs are among the most common infectious diseases, with annual costs estimated to be higher than $1.5 billion in the USA [4]. The incidence of UTIs worldwide is estimated to be up to 250 million cases per year [5]; 40–50% of women in the USA [4]. The incidence of UTIs worldwide is estimated with annual costs estimated to be higher than $1.5 billion most frequently caused by uropathogenic Escherichia coli [3].

Patient summary: Although antibiotic therapy is primarily used for the management of urinary tract infections (UTIs), misuse and overuse of antibiotics are of concern. Adherence to the international guidelines is important to prevent the spreading of antibiotic resistance. Clinical evidence confirms that the use of glycosaminoglycans is a valuable therapeutic approach to prevent UTI recurrence and limit the onset of antibiotic resistance.

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2. Evidence acquisition

In this narrative review and expert meeting report, the authors first performed a literature search on the currently available guidelines for UTI management, then analyzed the results of a European survey among urologists, and finally discussed the evidence during a symposium at the occasion of the European Association of Urology (EAU) Congress 2021. For the literature search, the keywords used were “UTIs/rUTIs” and “guidelines”; clinical trials, cohort studies, and systematic reviews were excluded. The literature databases consulted were PubMed and Cochrane Library; the results of the past 5 yr were considered. Concerning the survey, the authors reported the results of a
structured questionnaire administered to 227 urologists during the EAU/European Lower Urinary Tract Symptoms (ELUTS)/International Society for the Study of Bladder Pain Syndrome (ESSIC) meetings in 2018 to assess real-world prescribing patterns and their opinions on antibiotic resistance. Descriptive statistics was used to analyze the results, providing the percentage of the answers to each question. Finally, the authors, constituting an expert panel, discussed the evidence in the satellite symposium Are recurrent urinary tract infections a problem in urology? Facts and fiction held on July 10, 2021, during the virtual congress of the EAU.

### 3. Evidence synthesis

#### 3.1. What do EAU guidelines say for the management of rUTIs?

The literature search showed that there are several guidelines available providing recommendations for the management of UTIs. Despite some differences, all guidelines recommend the use of antimicrobial treatments for the acute phase of UTIs, and lifestyle advice, antimicrobial prophylaxis, and nonantimicrobial treatment for the prophylaxis of this infectious disease. With over 16 000 members, EAU is the leading European scientific society on urological practice. The EAU guidelines are endorsed by >70 national societies and scientific organizations including the 27 EU Member States. The EAU guidelines are frequently searched on the Internet, registering >355 000 visits in 6 mo.

The guidelines of the EAU are based on three pivotal concepts for a correct use of antimicrobial prophylaxis: (1) knowledge of the local pathogen profile and antimicrobial resistance, (2) careful evaluation of patient-related risk factors for the development of infectious complications after urological procedures, and (3) adherence to the EAU guidelines on urological infections. The guidelines provide a detailed and updated table summarizing the first-line treatments and alternatives together with the daily dose and the duration of the therapy for UTIs (Table 1) [16].

The guidelines also considered the role of fluoroquinolones, taking into account the characteristics of this class of antibiotics [26] and the increasing concerns about their safety [27,28]. Fluoroquinolones are broad-spectrum antibiotics and can be used for both Gram-positive and Gram-negative bacteria [26]. These are widely used in urology and for acute uncomplicated cystitis, but despite their popularity, there is an increasing concern regarding the potential severe side effects associated with this class of antibiotics [27]. On October 5, 2018, the European Medicines Agency Pharmacovigilance Risk Assessment Committee recommended restriction of the use of these antibiotics due to the possibility of persistent adverse effects. Over the past decade, the US Food and Drug Administration (FDA) also raised a series of warnings to underline the serious and disabling adverse events associated with fluoroquinolone use. Moreover, in 2018, the FDA required modifications to the labeling of all systemic fluoroquinolones to reinforce warnings about the risk of severe hypoglycemia and mental health effects associated with their use. On March 11, 2019, the European Commission made the regulatory conditions about the use of fluoroquinolones more stringent due to their disabling and potentially long-lasting side effects [28]. The EAU guidelines strongly recommend against the use of aminopenicillins or fluoroquinolones to treat uncomplicated cystitis. However, in uncomplicated cystitis, a fluoroquinolone can be used when the use of other antibacterial agents that are commonly recommended for the treatment of these infections is considered inappropriate [16]. The perioperative antimicrobial prophylaxis according to the EAU guidelines reduces antimicrobial usage without increasing postoperative infection rates, lowers the prevalence of resistant uropathogens, and is cost effective [29]. Unfortunately, the adherence to the EAU guidelines is not optimal. Antimicrobials are often used without a sound rationale, and evidence suggests that >50% of clinicians do not follow the guidelines for the use of antimicrobial agents [30–32]. The literature search outlined that there are several differences between EAU guidelines and American Urological Association/Canadian Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction guidelines, leading to contradictory and inconsistent recommendations [33].

#### 3.2. Assessing real-world prescribing patterns and opinions on antibiotic resistance: results from a European-wide survey

A survey about the management of rUTIs in the clinical practice was conducted on 277 urologists during EAU/ELUTS/ESSIC meetings in 2018. Data were collected using a structured questionnaire consisting of 11 questions (Table 2). The analysis of the survey respondents showed

### Table 1 – First-line treatments and alternatives together with the daily dose and the duration of the therapy for UTIs recommended by the EAU guidelines [16]

| Antimicrobial                                      | Daily dose       | Duration of the therapy (d) |
|---------------------------------------------------|------------------|-----------------------------|
| **First line**                                    |                  |                             |
| Fosfomycin trometamol                              | 3 g SD           | 1                           |
| Nitrofurantoin macrystal                           | 50–100 mg q.i.d. | 5                           |
| Nitrofurantoin monohydrate/macrystal               | 100 mg b.i.d.    | 5                           |
| Nitrofurantoin microcrystal ER                     | 100 mg b.i.d.    | 5                           |
| Pivmecillinam                                      | 200 mg t.i.d.    | 3–5                         |
| **Alternatives**                                   |                  |                             |
| Cephalosporins (eg. cefadroxil)                    | 500 mg b.i.d.    | 3                           |
| If the local resistance pattern for E. coli is <20%|                  |                             |
| Trimethoprim                                       | 200 mg b.i.d.    | 5                           |
| Trimethoprim–sulfamethoxazole                      | 160–180 mg b.i.d.| 3                           |

b.i.d. = bis in die (twice a day); EAU = European Association of Urology; q.i.d. = quarter in die (four times a day); SD = single dose; UTI = urinary tract infection.
Table 2 – The management of rUTIs in clinical practice: answers to a survey

| Number | Question                                                                 | Options                                                                 | Frequency (%) |
|--------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------|
| 1      | How many patients with an episode of lower UTI do you see in your clinical practice in 1 mo? | <20 | 16.3 |
|        |                                                                          | 20–50 | 55.9 |
|        |                                                                          | 50–100 | 19.4 |
|        |                                                                          | >100 | 8.4 |
| 2      | In your opinion, out of 100 patients affected by UTI, how many patients present an rUTI in your clinical practice? | 0–20 | 35.7 |
|        |                                                                          | 21–40 | 39.6 |
|        |                                                                          | 41–60 | 12.8 |
|        |                                                                          | 61–80 | 7.9 |
|        |                                                                          | 81–100 | 0.9 |
|        |                                                                          | No answer | 3.1 |
| 3      | When do you usually start antibiotic therapy for the treatment of an rUTI episode? | Always after the antibiogram test | 40.5 |
|        |                                                                          | As soon as possible, without waiting for antibiogram/culture results | 43.6 |
|        |                                                                          | Other | 13.7 |
|        |                                                                          | No answer | 2.2 |
| 4      | Which of the following antibiotic therapies do you usually prescribe for the management of an rUTI episode? | Amoxicillin/clavulanic acid | 7.5 |
|        |                                                                          | Ampicillin | 0.4 |
|        |                                                                          | Cotrimoxazole | 4.0 |
|        |                                                                          | Fosfomycin | 16.7 |
|        |                                                                          | Nitrofurantoin | 11.9 |
|        |                                                                          | Pivmecillinam | 3.1 |
|        |                                                                          | Trimethoprim alone or combined with sulfonamides | 3.5 |
|        |                                                                          | Other | 51.5 |
|        |                                                                          | No answer | 1.3 |
| 5      | How often have you had to change antibiotic therapy during the treatment of an rUTI episode? | Always | 1.8 |
|        |                                                                          | Often | 17.6 |
|        |                                                                          | Sometimes | 66.5 |
|        |                                                                          | Rarely | 13.7 |
|        |                                                                          | Never/almost never | 0 |
|        |                                                                          | No answer | 0 |
| 6      | Do you consider antibiotic resistance a relevant problem in your clinical practice? | Yes, extremely relevant | 40.1 |
|        |                                                                          | Yes, quite relevant | 36.6 |
|        |                                                                          | Yes, moderately relevant | 20.3 |
|        |                                                                          | No, not relevant at all | 1.8 |
| 7      | In your opinion, what has been the trend of antibiotic resistance in your clinical practice in the past 10 yr? | Significantly increasing | 18.9 |
|        |                                                                          | Slightly increasing | 68.3 |
|        |                                                                          | Basically unchanged | 4.8 |
|        |                                                                          | Slightly decreasing | 2.2 |
|        |                                                                          | Significantly decreasing | 3.5 |
|        |                                                                          | No answer | 2.2 |
| 8      | Do you prescribe antibiotics for the prophylaxis of rUTIs in your clinical practice? | No | 38.3 |
|        |                                                                          | Yes | 60.3 |
|        |                                                                          | No answer | 1.3 |
| 9      | Do you adopt nonantibiotic methods for the prophylaxis of rUTIs in your clinical practice? | No | 23.8 |
|        |                                                                          | Yes | 72.7 |
|        |                                                                          | No answer | 3.5 |
| 10     | Based on your experience, how do you rate the efficacy of these nonantibiotic treatments in rUTI management? | No answer | 29.5 |
|        | (a) Endovesical instillation of a combination of hyaluronic acid and chondroitin sulfate | Never prescribed | 28.2 |
|        |                                                                          | Not effective | 3.5 |
|        |                                                                          | Moderately effective | 25.1 |
|        |                                                                          | Extremely effective | 13.7 |
|        | (b) Endovesical instillation of chondroitin sulfate | No answer | 38.8 |
|        |                                                                          | Never prescribed | 28.2 |
|        |                                                                          | Not effective | 6.2 |
|        |                                                                          | Moderately effective | 21.1 |
|        |                                                                          | Extremely effective | 5.7 |
|        | (c) Endovesical instillation of hyaluronic acid | No answer | 30.8 |
|        |                                                                          | Never prescribed | 20.7 |
|        |                                                                          | Not effective | 6.2 |
|        |                                                                          | Moderately effective | 27.8 |
|        |                                                                          | Extremely effective | 14.5 |
|        | (d) Prophylaxis with D-mannose | No answer | 35.7 |
|        |                                                                          | Never prescribed | 20.7 |
|        |                                                                          | Not effective | 6.2 |
|        |                                                                          | Moderately effective | 29.1 |
|        |                                                                          | Extremely effective | 8.4 |
|        | (e) Prophylaxis with cranberry | No answer | 23.3 |
|        |                                                                          | Never prescribed | 6.2 |
|        |                                                                          | Not effective | 14.5 |
|        |                                                                          | Moderately effective | 44.9 |
that 76.7% were European and 55.9% were <46 yr old. The most frequent countries of origin are shown in Table 3 (for the complete list of nationalities, see Supplementary Table 1). Most clinicians (55.9%) reported to visit from 20–50 patients affected by lower UTIs per month and that up to 40% of these patients were suffering from rUTIs. The antibiotics remain the cornerstone for the treatment of UTIs, although in clinical practice, they are often used on an empirical basis pending urine culture [34–36]. In particular, 40.5% of participants reported waiting for an antibiogram test and 43.6% reported starting the antibiotic treatment as soon as possible. International literature frequently reports an inappropriate use of fluoroquinolones and quinolones for UTIs [35,37]. The survey showed that fluoroquinolones and quinolones are still used by clinicians (these were included in the reply “other” of question 4, corresponding to 51.5%). Of the respondents, 66.5% reported that they had to change the antibiotic therapy at least “sometimes”. Noteworthy, participants are aware of the problem represented by the resistance to antibiotics (40% of them defined it “extremely relevant”). Of the respondents, 68% noted a slight increase in the trend of antibiotic resistance, while 20% defined it “significantly increasing.” Yet, 60% of clinicians reported to prescribe antibiotics for the prophylaxis of rUTIs. Most of respondents (72.7%) reported to prescribe nonantibiotic methods for the prophylaxis of rUTIs. Details and percentages of the different alternative methods used are reported in Table 2. Urologists above and below 45 yr of age gave similar answers to the questionnaire.

### 3.3. Glycosaminoglycan therapy: a real alternative to antibiotics for the prevention of rUTIs

The satellite symposium Are recurrent urinary tract infections a problem in urology? Facts and fiction held on July 10, 2021, during the virtual congress of the EAU, discussed the role of glycosaminoglycan (GAG) therapy as an alternative to antibiotics for the prevention of rUTIs.

In the 1980s, antibiotics protected us from different types of infections. Today, antibiotic resistance fosters the spread of infectious diseases. To overcome this issue, there are two possible approaches. The first one is finding new antibacterial drugs, and yet very few of such medications are being approved. Alternatively, we could change our point of view. Indeed, medicine is changing as life expectancy is increasing; patients are changing too, becoming older and suffering from more comorbidities, and bacteria are changing as well.

In the management of UTIs, a prompt diagnosis, risk identification and early treatment are essential to reduce the number of symptomatic episodes, the level of stress and anxiety of the patients, and the number of unnecessary antibiotics. Recently, Cai et al. [2,38] developed and validated a nomogram that has been proved easy to use and accurate in predicting the recurrence risk in women affected by rUTIs. Nomogram variables included the number of partners, bowel function, type of pathogens isolated (Gram-positive/negative), hormonal status, number of previous UTI recurrences, and previous treatment of asymptomatic bacteriuria (Fig. 1).

Considering the evident limits of the antibiotics for the prevention of episodes of rUTIs, alternative treatments focus on the relationship between bacteria and host.
Bladder epithelium is a specialized tissue protected by GAGs, such as HA and CS [39]. The GAG layer is a protective barrier, preventing damaging substances found in the urine from penetrating into the deeper layers of the bladder wall [40]. The presence of an intact GAG layer covering the urothelium prevents bacteria (especially *E. coli*) from penetrating the bladder, and attacking and destroying urothelial cells (Fig. 2).

A deficit in the GAG layer is the first step in developing chronic inflammatory diseases of the bladder [41]. As a mat-
In conclusion, adherence to the international guidelines seems to be a promising nonantibiotic therapy to prevent rUTIs. Importantly, the safety profile of this combination has been reported to be very favorable, without adverse events of particular significance.

4. Conclusions

This paper summarizes the EAU recommendations for the treatment of UTIs/rUTIs, presents data on the adherence to the recommendations, and discusses the evidence on the use of HA + CS in the prophylaxis of rUTIs.

The main limits of this paper are that it is focused on the European approach, and that the survey and its statistical analysis are still preliminary.

The strengths of this paper are that the issues are discussed from different perspectives, as the work is the result of a multinational and multidisciplinary panel of authors. In addition, the survey and the symposium give valuable insight into the attitude of physicians treating UTIs. As a result of the abovementioned considerations, the authors, as far as clinical practice is concerned, recommend performing urine culture for each symptomatic rUTI to investigate the type of bacteria affecting the patient's bladder. Different bacterial species may be the cause of subsequent episodes of UTIs in the same patient. Moreover, several pathologies can show an overlap in the type of bacteria involved.

The survey showed that amoxicillin, fosfomycin, and nitrofurantoin, alone or in combination, are the most prescribed antibiotics. The authors, adding recent information, reported that, in the country most represented in the survey (Italy), there are two scenarios: clinicians prescribing fluoroquinolones alone or fluoroquinolones in combination with cephalosporins or GAGs in the relapses. One point of reflection is the weight that economic or legal concerns may have in the choice of physicians to prescribe antibiotics despite the awareness of the resistance issue.

The authors, commenting on the available data, observed that GAG therapy is an effective alternative treatment to antibiotics. About the intravesical administration of GAGs, the authors suggest one instillation per week, two instillations per month, and one instillation per month until the patient's recovery. With this approach, the authors obtained good adherence to the schedule and improved QoL of the patients. Table 4 summarizes the considerations and recommendations emerged during the symposium.

In conclusion, adherence to the international guidelines is important to align the clinical practice and avoid the
spreading of antibiotic resistance. The survey outlines that the misuse and overuse of antibiotics are major problems; the clinical evidence confirms that GAG therapy is a valuable approach to prevent the recurrence of the episodes of UTIs and to limit the onset of antibiotic resistance.

**Author contributions:** Franck Bruyere 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:** Bonkat, Cai, Galeone, Koves, Bruyere.

**Acquisition of data:** Bonkat, Cai, Galeone, Koves, Bruyere.

**Analysis and interpretation of data:** Bonkat, Cai, Galeone, Koves, Bruyere.

**Drafting of the manuscript:** Bonkat, Cai, Galeone, Koves.

**Critical revision of the manuscript for important intellectual content:** Bonkat, Cai, Galeone, Koves, Bruyere.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.07.009.

**Table 4 – Clinical remarks emerged from the symposium**

| Background | UTIs are very common; many women suffer from rUTIs |
| Real-world prescribing patterns | Of the responders, >40% reported that they start antibiotic therapy for the treatment of an rUTI episode as soon as possible (without waiting for antibiogram/culture results) |
| | Changing antibiotic therapy during the treatment of an rUTI episode is frequent |
| | Antibiotic resistance is considered a relevant problem (extremely relevant 40%) |
| | Of the urologists involved in the survey, 60% prescribe antibiotics for the prophylaxis of rUTIs |
| | Of the urologists involved in the survey, >70% prescribe nonantibiotic methods for the prophylaxis of rUTIs and declare that they will continue or start to prescribe nonantibiotic treatment |
| | Intravesical instillation of HA alone or in combination with CS and probiotics is the nonantibiotic treatment considered most effective by the responders |

**CAG therapy**

- Safe and useful in the management of patients with recurrent UTIs
- Promising to improve patient's QoL
- Decrease in the number of UTI recurrences
- Improve the adherence to antimicrobial stewardship

**CS** = chondroitin sulfate; **GAG** = glycosaminoglycan; **HA** = hyaluronic acid; **QoL** = quality of life; **rUTI** = recurrent UTI; **UTI** = urinary tract infection.

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