Stone Disease

European Association of Urology Urolithiasis Guidelines: Where Are We Going?

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Abstract

Urolithiasis is a clinical condition showing increasing trends, especially among European and other developed countries. The European Association of Urology (EAU), in close collaboration with experts in the field, publishes a yearly updated clinical guideline, in order to provide practicing urologists around Europe and the rest of the world a tool for optimizing patient care and decision-making. The methodological approach for developing this guide is quite rigorous and follows rigorous scientific standards. The challenges that a urologist faces are increasing; therefore, during meticulous literature search, the EAU Urolithiasis Panel identifies gaps in knowledge and conducts systematic reviews, in order to provide answers or to propose ideas for designing future research. This way, a new section was published last year, regarding diagnosis and management of bladder stones, with more systematic reviews on the way. The aim of this study is to analyze current structure and goals of the EAU Urolithiasis Panel, along with future ambitions and challenges.

Patient summary: Increasing trends in kidney stone disease along with developments in technology necessitate systematic organization of information for urologists in order to be able to follow diagnostic and therapeutic algorithms for optimizing patient care. The role of the European Association of Urology Urolithiasis Guideline Panel is to provide such a tool by development of urolithiasis guidelines on an annual basis.

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1. Introduction

Modern medicine and clinical practice are based on solid evidence, after the valuable introduction of this concept by Gordon Guyatt [1] back in 1990. The European Association of Urology (EAU), loyal to the principles of evidence-based medicine, publishes a yearly updated guideline, in close collaboration with experts in the field. This comprehensive guide is a valuable tool for practicing urologists and presents the highest level of evidence, after proper criticism is performed, to detect potential faults and to propose areas for future research of improved quality and methodological integrity.

Urolithiasis prevalence in Europe shows an increasing trend and ranges between 5% and 9% [2]. Urolithiasis guidelines, first published in 2000, provide a clinical guide for urologists, focusing on prevention, diagnosis, and medical or surgical management of stone disease, updated on a

yearly basis. This study objective is to analyze the aim and current form of urolithiasis guidelines, while also demonstrating future ambitions and goals set by the panel members.

2. Panel synthesis and organization

2.1. The present

The EAU Urolithiasis Guidelines Panel consists of a group of six renowned, international urologists with expertise in the management of patients with stone disease, who have contributed to the existing knowledge on the field with contemporary and innovative studies. Panel associate members accompany this team of experts and are guided by their seniors, in order to conduct a number of new systematic reviews (SRs) and also aid in the annual update of the guidelines through literature search.

2.2. The future

The EAU Panel is aware of the fact that several detailed questions need to be answered in cooperation with specialists from other disciplines; for example, literature search regarding association between creatinine elevation, progressive kidney function loss, and potential end-stage renal disease reveals abundant data, mainly derived from observational studies, which support an increased risk of kidney function loss in stone formers, when compared with normal individuals. This may partially be explained by the shared common risk factors of these two conditions, such as hypertension, diabetes mellitus, obesity, and metabolic syndrome [3]. Other pathogenic mechanisms, such as renal vasoconstriction with reduced glomerular filtration rate due to ureteral obstruction [4], chronic infectious processes [5], and abnormal remodeling with increased levels of transforming growth factor beta/tumor necrosis factor-alpha production and fibroblast accumulation [5], may also be incriminated. Therefore, the idea for involving a nephrologist with clinical expertise to metabolic kidney diseases is under consideration by panel members, in order to maximize the effectiveness of protective measures proposed by the guidelines. An experienced nephrologist may also suggest the necessary clinical steps for the practicing urologist to adopt regarding follow-up of kidney function and the proper time for a nephrology referral to be performed.

Traditional medicine follows a paternalistic pattern, but fortunately during the last decades, a shift is noticed to a more patient-centered approach, especially after the recognition of the great importance of patient quality of life. Therefore, patient engagement in the process of guideline development is now proposed by the Guidelines International Network [6,7]. Involvement of a patient representative will aid in the key steps of a guideline development, such as the feasibility of the proposed measures from the patient side and factors affecting adherence, recognition of patient-related issues, and dissemination of the guideline to a wider audience in order to gain access to a greater pool of data, especially for topics where randomized trials cannot be conducted. Therefore, the Urolithiasis Panel, along with several panels of the EAU Guidelines Office (GO), plans to involve a patient representative on board for the development of future editions.

3. Aims and methodological approach of the Urolithiasis Panel

3.1. The present

The EAU GO expects from each subspecialty panel to browse existing literature, identify the most high-quality studies, and provide recommendations regarding several aspects of the respective medical condition. For this reason, a set of methodological scientific standards is established and expected to be followed by all panels under the auspices of EAU GO, including the Urolithiasis Panel (Table 1).

Unlike American Urological Association (AUA) guidelines, which are not updated annually, but according to novel data availability, and are based solely on the conduct of SRs and meta-analyses by AUA members, the EAU Panel selects every year qualitative SRs, and randomized and high-quality observational studies in areas with scant literature, and make appropriate recommendations after critical appraisal by all members. An important difference

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### Table 1 – Summary of the present situation and future goals of the Urolithiasis Panel

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AUA = American Urological Association.
regarding the development process is the synthesis of an ad hoc panel, which is new in AUA for every new guideline process, while in EAU it has permanent members, who slowly rotate and give a character of continuity. Data collection (including acquisition, synthesis, and final guideline production) follows a methodologically sound pathway and reporting standard, with the main principles adopted by the Cochrane Collaboration [8]. In cases where literature does not provide answers to the existing clinical questions or the data are out of date, the panel formulates a concise PICO format after discussion and shared decision, and after the approval of the GO Methodology Committee, the associate members under the guidance of their seniors proceed with protocol development and literature search, data analysis, risk of bias assessment, writing of manuscript, and publishing of the results [9]. The results of these SRs may not always be informative in providing a definitive answer to the question, but their role may be to reveal gaps in knowledge and ultimately propose ideas for researchers to conduct future randomized controlled trials (RCTs). Both associations provide grade of recommendations for their suggestions, but in the AUA document, reader can find five levels of strength, while the EAU document has two levels of strength. Finally, the presentation of data differs between the two associations; it is based on clinical questions with index patients in the AUA guidelines, while in EAU guidelines, data are presented as a comprehensive textbook with supporting flowcharts (Table 2).

The panel group publishes its recommendations according to a hierarchical order based on the quality of existing evidence. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system used for this purpose has proved its efficiency and transparency throughout the years in several circumstances [10].

Creation of EAU urolithiasis guidelines needs, as analyzed before, critical appraisal and judicious use of existing literature. This procedure inevitably entails a degree of subjectivity, reflected in the recommendations and their grading. This fact, combined with different methodological approaches, explains potential deviations between EAU and AUA guidelines. In a recent study, Pradère et al [11] used the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument to detect points of consensus and disagreements, along with assessing the quality of existing international guidelines for surgical management of urolithiasis. As expected, the most complete guidelines came from the EAU and the AUA, along with the Societe Internationale d’Urologie (SIU)/International Consultation on Urological Diseases (ICUD). The authors rated both EAU and AUA guidelines with satisfying scores of 71% and 75%, respectively [11]. They detected different cutoff sizes for expectant management of ureteral stones, which were reported to be 10 mm in AUA [12,13] and 6 mm in EAU [14] guidelines; regarding medical expulsive therapy with α-blockers, EAU recommends it mainly for ureteral stones of lower ureter >5 mm in size, while AUA recommends it only for distal ureteral stones [11]. Specifically for follow-up of these patients, AUA guideline advises an interval of 4-6 wk for active monitoring [12,13]. In conclusion, authors report that despite different methodological approaches, the two guidelines show consensus on most clinical questions with minor heterogeneity [11].

3.2. The future

Biomedical research productivity, in terms of yearly published studies, is shown by the steep increase of publications, along with an increased number of peer-reviewed journals (nearly 30 000). This literature wealth necessitates a constant update of guidelines, in order to provide clinicians the most recent knowledge to assist them in decision-making. The EAU Guidelines Urolithiasis Panel performs a yearly literature search in broadly used databases, such as PubMed/EMBASE, Ovid, and Cochrane Library, using relative search terms for stone disease. After the initial screening of studies, usually by associate members, panel experts perform a critical appraisal of the full text of studies and select the most appropriate ones to be

<table>
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<td><strong>AUA</strong></td>
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<td>Ad hoc panels for each new guideline process</td>
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<td>Complete systematic reviews with wide scope</td>
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<td>Strong level of evidence rating</td>
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**AUA** = American Urological Association; **EAU** = European Association of Urology; **GRADE** = Grading of Recommendations, Assessment, Development and Evaluation.
considered for inclusion and changes/additions in the updated version. In parallel, each member is assigned with specific parts of the guideline, and after detailed discussion and review, corrections are made. Outdated references may be deleted during this stage. As an additional “security level”, panel members aim to perform regular reassessment of recommendation grading and propose areas with space for improvement, via conducting RCTs and SRs within the urological community.

Specifically, in the 2020 version, a limited update of recommendations was performed. In the diagnostic workup plan for patients presenting to the emergency department with symptomatic urolithiasis, spot urine sample dipstick and measurement of serum blood creatinine, uric acid, calcium, sodium, potassium, and C-reactive protein/com- plete blood cell count are advised to be performed with a weak, instead of a strong, level of recommendation, as mentioned in the previous version [14,15]. Shockwave lithotripsy (SWL) still represents a viable therapeutic option for the management of renal stones due to its noninvasive nature and acceptable success rates, if certain criteria apply. Stone density, expressed in Hounsfield units (HU) in non-contrast computed tomography (NCCT) scan, and heterogeneity (index) are main imaging parameters, which can affect stone-free rates [16]. Therefore, panel members have rephrased a previous recommendation to emphasize that when evaluating a patient preoperatively for stone removal, besides medical history and potential previous stone analysis, the HU in NCCT should be considered carefully. In patients with stones of density >1000 HU, especially if homogeneous, the expectation of success with SWL should be lowered [14].

Management of urolithiasis after numerous technological advances and innovations during the previous years is mostly minimally invasive. Instrumentation and familiarity with all the ancillary equipment are important for the successful and uneventful completion of an endourological procedure. Current versions of urolithiasis guidelines focus on the diagnosis and management of stone disease by making recommendations on indications and risks of several types of surgery. Along with the existing chapters about “best clinical practice” for each technology (SWL, ureteroscopy, and percutaneous nephrolithotomy), panel members are considering to incorporate, in future versions, a section dedicated to the description and proper use/maintenance of several parts of endourological equipment in the operating room, for example, flexible/semirigid ureteroscopes/cystoscopes, laser fibers and their setting, types and proper use of guidewires, baskets, and graspers.

In the 2020 urolithiasis guideline version, it is advised to follow up patients with asymptomatic renal stones using ultrasound (U/S), -ray, or computed tomography (CT) scan of the kidneys, ureters, and bladders, which gradually becomes more sparse in the absence of recurrence (initially every 6 mo after initial stone event and annually afterward) [14]. A great debate exists in the urological community regarding the necessity of follow-up and the time intervals for patients with upper urinary tract lithiasis. A randomized trial reported similar clinical outcomes in terms of ancillary treatment requirement, stone-free rates, kidney function, and symptomatic episodes during a 2-yr follow-up, irrespective of whether observation or treatment with SWL was performed for patients with asymptomatic calyceal stones <15 mm [17]. Bearing in mind that after 5 yr, roughly 50% of patients with asymptomatic renal stones will experience some form of symptoms [18] and also the lack of high-level evidence in follow-up after receiving treatment for urolithiasis, both in the EAU and the AUA version, the EAU Panel decided to perform a relevant SR. This review will aim to systematize knowledge about whether scheduled follow-up offers any clinical benefit in patients who undergo definitive treatment of upper urinary tract stones. The definite goal of the panel is to detect existing knowledge on this topic and aid clinicians to optimize patient follow-up; however, in case of a lack of evidence, proposals will be made for future clinical research.

4. Bladder stone guidelines

4.1. The present

In 2019, a subpanel of the Urolithiasis Panel was created, which released the guidelines on bladder stones. The incidence of bladder stones is relatively low, roughly 5% of the total number of urinary tract stones [19], and peaks at 3 yr in children in developing countries and at 60 yr in adults, with an observed increased male-to-female ratio [20]; however, they can still lead to high rates of morbidity and mortality. This guideline was updated in 2020 in the form of grade of recommendation revision and rephrasing. In short, U/S is the modality of choice, with a strong grade of recommendation for initial screening of both adults and children with bladder stones, while CT scan or cystoscopy should strongly be considered in case of negative U/S or if there is an additional clinical suspicion for upper urinary tract lithiasis or other indolent pathology [20]. The clinician should also include uroflowmetry, postvoid residual volume, urine culture, and metabolic evaluation in the diagnostic algorithm [20]. Regarding treatment, oral chemolysis with close urine pH monitoring is still a choice if uric acid stone is the culprit, while transurethral cystolithotripsy with a nephroscope/ resectoscope is the best form of surgical treatment [20]. In selected cases, open cystolithotomy or laparoscopic surgery as well as percutaneous cystolithotripsy may be considered, while SWL does not offer high stone-free rates [20].

4.2. The future

Following the general principles of the EAU GO, the Panel of Bladder Stones quickly realized a lack of systematic knowledge regarding bladder stone treatment in children. The most common type of bladder stone in children is primary, mainly due to poor hygiene and nutritional status, mostly in the developing world and in patients of low socioeconomic status [21]. Current literature reveals high morbidity and mortality rates [19]; therefore, it is important to provide clinicians a guide on benefits and harms of several treatment options (transurethral/percutaneous cystolithotripsy,
open or laparoscopic cystolithotomy, and SWL) in children, to enhance confidence in clinical decision-making and maximize benefits for patients. The review will focus on studies including children/adolescents < 18 yr of age with any type of bladder stone, and compare surgical treatment options regarding safety and efficacy. Randomized trials, and prospective or retrospective comparative studies will be eligible, in contrast to noncomparative studies.

5. Conclusions

The EAU Urolithiasis Panel in collaboration with GO represents a relatively small, but highly active, group of international experts. The productivity is reflected in high-quality publications in peer-reviewed journals, but most importantly in annual release of an updated version of the guidelines, based on the highest level of evidence in the literature. This condensed work aids urologists in evidence-based clinical decision-making and identifies gaps in knowledge for future research, such as the type and optimal frequency of follow-up in patients with urolithiasis after receiving treatment, or the benefits and harms of treating bladder stones in children. The high level of consensus with AUA guidelines, despite a different methodological approach, further reflects the methodological integrity and high quality of evidence produced.

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Study concept and design: Tzelves, Türk, Skolarikos.

Acquisition of data: Tzelves, Türk, Skolarikos.

Analysis and interpretation of data: Tzelves, Türk, Skolarikos.

Drafting of the manuscript: Tzelves, Türk, Skolarikos.

Critical revision of the manuscript for important intellectual content: Tzelves, Türk, Skolarikos.

Statistical analysis: Tzelves, Türk, Skolarikos.

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