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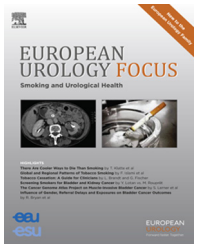

Grey Zone – Stone Disease

Grey Zones in Urolithiasis Guidelines

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1. Background

The European Association of Urology (EAU) Guidelines were originally introduced to the urology community in 2000. The EAU convened panels of experts for every urology field they aimed to cover in the years to follow. The current Urolithiasis Panel works in the era of randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses (MA), identifying relevant literature via structured searches of Medline, EMBASE, and Cochrane Library databases [1]. However, there are specific questions and controversies that cannot be answered based on the available RCTs, SRs, and MAs, either because of contradicting results or for the simple reason that the studies conducted were not of adequate quality, resulting in a lack of evidence. In such cases, panel expertise is the key component in the recommendation grade (sometimes resulting in a higher grade [upgrading] of a recommendation provided in the guidelines). Using the current urolithiasis guideline as a reference [1], some topics concerning the diagnosis and treatment of urolithiasis are highlighted here as grey zones in urolithiasis.

2. Grey zones in urolithiasis because of lack of evidence

2.1. Risk groups among stone formers

On the basis of the recurrence rate of stone formation, low-risk and high-risk patient groups have been defined [1]. At first glance the underlying references seem to be recent ones; however these publications themselves rely on older studies with low-level evidence. Besides, in recent years the importance of genetic influences in stone recurrence has become more evident and needs to be monitored [2].

2.2. Diagnostic evaluation

There are three panel upgrades in the diagnostic imaging section of the current urolithiasis guidelines. The Urolithiasis Panel highly recommends immediate imaging in a stone patient presenting with fever, a solitary kidney, or a doubtful diagnosis. Although self-evident, the impact of immediate scanning and the type of imaging modality on treatment outcomes has never been questioned in a comparative study.

In align to the aforementioned speculation the panel, despite the low evidence existing, highly recommends to perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed. It remains to be proven by a RCT whether a non-contrast imaging will lead to the same stone-free rate (SFR) without increasing the complication rate of an intervention.

Pregnancy represents an exception to the above rule. Although ultrasound cannot differentiate between ureteral obstruction and the normal physiological changes occurring in pregnancy, this imaging modality has been highly recommended to be the preferred method of imaging in pregnant women. It is doubtful whether a comparative study could ever be performed in pregnant women.

The exact diagnostic biochemical work-up for emergency and non-emergency urolithiasis patients has not been clarified in the literature. Recommendations on urine

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examination, for example, are based on two reviews from 2005 and 2009, an AWMF Guideline [16] that has recently expired, and a 2008 consensus meeting [3,4]. The EAU guidelines on urinary infection [5] recommend urine culture rather than (automated) microscopy, although the evidence supports (automated) microscopy and dipstick analysis. However the underlying references are only one observational and one comparative study [6,7].

Overall there is a lack of trials on the most reliable and effective method for appropriately addressing urinary infections and metabolic parameters during metabolic work-up for stone patients.

2.3. Disease management

For patients who present with sepsis and an obstructed urinary system, the panel highly recommends collection of urine for antibiotic testing following decompression, immediate initiation of antibiotic therapy, and re-evaluation of the antibiotic regimen according to urine culture findings. Among the few trials addressing decompression technique (ureteral catheter vs percutaneous nephrostomy), only Pearle et al [8] mention the urine culture findings after decompression. Although clinically well accepted, the impact of this second antibiogram on treatment outcomes has not yet been evaluated to our knowledge.

2.4. Observation of renal stones

Asymptomatic caliceal stones may be observed according to the guidelines. However, there is uncertainty regarding follow-up frequency and methods. On the basis of expert opinion, the guidelines recommend initial follow-up after 6 months and then yearly (grade of recommendation A). There are no data supporting a specific imaging modality. Most of the literature on this topic consists of small, single-center observational studies, one of which was prospective [9] and one a single-center randomized study among 200 patients comparing prophylactic shockwave lithotripsy (SWL) and observation [10].

Other examples of insufficient literature support involve recommendations for chemolysis of stones, the use of baskets and intracorporeal lithotripsy devices during endourologic procedures, and the best clinical practice for several stone removal procedures.

3. Grey zones in urolithiasis despite supposed high-level evidence

Several topics represented by a large number of publications including RCTs and MAs that still remain in the grey zone. We have picked out two examples.

3.1. Medical expulsive therapy

Medical expulsive therapy (MET), in particular with α-blockers, has been recommended as supportive medication in the observational treatment of ureteral stones and after SWL. A huge number of RCTs and several MAs based on these trials have been published to date that support the use of α-blockers. However, a few recent high-quality, large multicenter placebo-controlled RCTs raised serious doubts about the effectiveness of α-blockers. This led to downgrading of the previous grade of recommendation for use of α-blockers from level A to level C. The existing high-level literature is controversial [11] and opens the problem of MET use for passage of stone fragments after SWL.

3.2. Selection of procedures for active stone removal

Debate is ongoing regarding the choice of procedure to actively remove urinary calculi. SWL compared to percutaneous nephrolithotomy (PNL) and ureteroscopy (URS), as well as the best clinical practice, has not been completely assessed yet. The impact of renal anatomy on the choice and outcome of stone removal techniques has been an active discussion topic until recently [12]. In an effort to provide the best evidence, the Urolithiasis Panel performed two SRs to identify the benefits and harms of the different percutaneous tract sizes (2945 abstracts screened, 18 studies included) and to compare URS with SWL in the treatment of upper ureteral stones (5380 abstracts screened, 47 studies included) [13,14]. Both studies provide the best available answers to particular questions, such as differences in bleeding rates between various renal tract sizes and differences in the stone-free rate between SWL and URS, but the results may still not be sufficient to establish strict recommendations owing to the number and quality of the studies available for review.

4. Conclusions

Grey zones in guideline work can arise from a lack of suitable literature or controversies in even highly rated publications. Unanswered clinical questions need to be addressed independently by well-designed, double-blind, placebo-controlled, multicenter RCTs with clearly defined end points.

The contradictory results between MAs of small RCTs and findings from large, well-conducted multicenter trials show the methodological vulnerability of MAs, in particular if small single-center and/or lower-quality studies have been included. Small single-center trials, for instance, tend to show greater treatment effects compared to multicenter RCTs [15]. This also highlights the responsibility involved in careful planning for an RCT. To avoid publication bias, only trials registered in advance should be accepted for publication. When performing MAs, the criteria for study inclusion should be defined very carefully.

Conflicts of interest: The authors have nothing to disclose.

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