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ORIGINAL PAPER

Management of urinary stones: State of the art and future perspectives by Experts in Stone Disease

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Summary

Aim: To present state of the art on the management of urinary stones from a panel of globally recognized urolithiasis experts who met during the Experts in Stone Disease Congress in Valencia in January 2024. Options of treatment: The surgical treatment modalities of renal and ureteral stones are well defined by the guidelines of international societies, although for some index cases more alternative options are possible. For 1.5 cm renal stones, both m-PCNL and RIRS have proven to be valid treatment alternatives with comparable stone-free rates. The m-PCNL has proven to be more cost effective and requires a shorter operative time, while the RIRS has demonstrated lower morbidity in terms of blood loss and shorter recovery times. SWL has proven to be less effective at least for lower calyceal stones but has the highest safety profile. For a 6mm obstructing stone of the pelviureteric junction (PUJ) stone, SWL should be the first choice for a stone less than 1 cm, due to less invasiveness and lower risk of complications although it has a lower stone free-rate. RIRS has advantages in certain conditions such as anticoagulant treatment, obesity, or body deformity.

Technical issues of the surgical procedures for stone removal: In patients receiving antithrombotic therapy, SWL, PCN and open surgery are at elevated risk of hemorrhage or perinephric hematoma. URS, is associated with less morbidity in these cases. An individualized combined evaluation of risks of bleeding and thromboembolism should determine the perioperative thromboprophylactic strategy. Pre-interventional urine culture and antibiotic therapy are mandatory although UTI treatment is becoming more challenging due to increasing resistance to routinely applied antibiotics. The use of an intrarenal urine culture and stone culture is recommended to adapt antibiotic therapy in case of postoperative infectious complications. Measurements of temperature and pressure during RIRS are vital for ensuring patient safety and optimizing surgical outcomes although techniques of measurements and methods for data analysis are still to be refined. Ureteral stents were improved by the development of new biomaterials, new coatings, and new stent designs. Topics of current research are the development of drug eluting and bioresorbable stents.

Complications of endoscopic treatment: PCNL is considered the most invasive surgical option. Fever and sepsis were observed in 11 and 0.5% and need for transfusion and embolization for bleeding in 7 and 0.4%. Major complications, as colonic, splenic, liver, gall bladder and bowel injuries are quite rare but are associated with significant morbidity. Ureteroscopy causes less complications, although some of them can be severe. They depend on high pressure in the urinary tract (sepsis or renal bleeding) or application of excessive force to the urinary tract (ureteral avulsion or stricture).

Diagnostic work up: Genetic testing consents the diagnosis of monogenetic conditions causing stones. It should be carried out in children and in selected adults. In adults, monogenetic diseases can be diagnosed by systematic genetic testing in no more than 4%, when cystinuria, APRT deficiency, and xanthinuria are excluded. A reliable stone analysis by infrared spectroscopy or X-ray diffraction is mandatory and should be associated to examination of the stone under a stereomicroscope. The analysis of digital images of stones by deep convolutional neural networks in dry laboratory or during endoscopic examination could allow the classification of stones based on their color and texture. Scanning electron microscopy (SEM) in association with energy dispersive spectrometry (EDS) is another fundamental research tool for the study of kidney stones. The combination of metagenomic analysis using Next Generation Sequencing (NGS) techniques and the enhanced quantitative urine culture (EQUC) protocol can be used to evaluate the urobiome of renal stone formers. Twenty-four hour urine analysis has a place during patient evaluation together with repeated measurements of urinary pH with a digital pH meter. Urinary supersaturation is the most comprehensive physicochemical risk factor employed in urolithiasis research. Urinary macromolecules can act as both promoters or inhibitors of stone formation depending on the chemical composition of urine in which they are operating. At the moment, there are no clinical applications of macromolecules in stone management or prophylaxis. Patients should be evaluated for the association with systemic pathologies.

Prophylaxis: Personalized medicine and public health interventions are complementary to prevent stone recurrence. Personalized medicine addresses a small part of stone patients with a high risk of recurrence and systemic complications requiring specific dietary and pharmacological treatment to prevent stone recurrence and complications of associated systemic diseases. The more numerous subjects who form one or a few stones during their entire lifespan should be treated by modifications of diet and lifestyle. Primary prevention by public health interventions is advisable to reduce prevalence of stones in the general population. Renal stone formers at "high-risk" for recurrence need early diagnosis to start specific treatment. Stone analysis allows the identification of most "high-risk" patients forming non-calcium stones: infection stones (struvite), uric acid and urates, cystine and other rare stones (dihydroxyadenine, xanthine). Patients at "high-risk" forming calcium stones require a more difficult diagnosis by clinical and laboratory evaluation. Particularly, patients with cystinuria and primary hyperoxaluria should be actively searched.

Future research: Application of Artificial Intelligence are promising for automated identification of ureteral stones on CT imaging, prediction of stone composition and 24-hour urinary risk factors by demographics and clinical parameters, assessment of stone composition by evaluation of endoscopic images and prediction of outcomes of stone treatments. The synergy between urologists, nephrologists, and scientists in basic kidney stone research will enhance the depth and breadth of investigations, leading to a more comprehensive understanding of kidney stone formation.

KEY WORDS: *Urinary calculi; Percutaneous nephrolithotomy; Retrograde intrarenal lithotripsy.*

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INTRODUCTION

(*Athanasios Papatsoris, Murtadha Al Musafer, Athanasios Dellis, Mohamed El Howairis*)

Urolithiasis in the urinary tract is a worldwide prevalent disease, affected from several factors, especially diet- and climate-related, that shows increasing prevalence in all ages, races, and sexes. They suggest a cause of significant morbidity despite scientific and technological advances. As a result, the assessment of optimal diagnostic pathways and evidence-based management of urolithiasis and their incorporation into clinical practice is of utmost importance. The purpose of this article is to accumulate up-to-date available knowledge and surgical tips and tricks from a panel of globally recognized urolithiasis experts who met during the *Experts in Stone Disease Congress in Valencia* in January 2024.

This global multi-disciplinary approach in Urolithiasis was Noor Buchholz's vision. It is with regret to accept that Noor is no longer with us, and this article is a least farewell.

Surgical stone management

The indications for the treatment of kidney and ureteral stones are well defined by the main guidelines (Table 1), although some borderline cases remain amenable to different forms of treatment (1-3). These conditions may include kidney stones of 15 mm diameter and stones of 6 mm in the pyelo-ureteral joint. Below are the potential benefits of each form of treatment.

Table 1.
Indications for treatment of 10-20 mm stones according to American and Europen associations guidelines.

Stone Location	Stone size	EAU guidelines	AUA guidelines
Upper/middle calyces/renal pelvis	10-20	PCNL/URS or SWL	SWL or URS
Lower pole	10-20 (favourable factors for SWL)	SWL or URS/PCNL	
	10-20 (unfavourable factors for SWL)	PCNL/URS as first line, SWL as second line	

The 1.5 cm kidney stone

Mini-PCNL (Elenko Popov)

It is well established in international guidelines that most renal stones > 2 cm in diameter should be treated with *percutaneous nephrolithotomy* (PCNL) and those with a diameter < 1-2 cm with RIRS; however, mini-PCNL constitutes a viable and effective minimally invasive treatment option for ever smaller stones, whereas the limits of RIRS are continuously pushed towards ever larger stones.

In order to decrease the complications rate of PCNL, *Jackman* (1998) (4) developed the concept of minimally-invasive percutaneous nephrolithotomy (mini-perc), which is based on the assumption that the decrease of PCNL tract size (< 16 Fr) will lower the trauma on the renal parenchyma and hence the risk of bleeding.

During the last decades, this tendency towards miniaturization (mini-PCNL, super-miniPCNL, ultra-mini PCNL and micro-PCNL) was steadily developed allowing for PCNL completion through a narrower and safer nephrostomy tract (5, 6).

A critical point for the success of this miniaturization was the introduction of medium and high-power lasers, which allows bigger stones to be treated with mini-PCNL The ongoing experience with the mini-PCNL technique showed that mini-PCNL is not only a miniaturization but also a different method to remove the stones, as the stones come out of the calyceal system only by means of the irrigation flow without any further need of forceps or baskets (vacuum-cleaner effect or active aspiration sheath).

Standard PCNL still represents "*the big gun*" to be used in cases of bulky nephrolithiasis being highly effective although with more significant complications (collateral damage). On the contrary miniaturized PCNL has the "*the special forces*" philosophy being small size, agile, flexible and with minimal surgical trauma. A significant decrease of transfusion rate was observed with mPCNL.

In the comparison with RIRS, new technological advancements favor the choice of mini-PCNL as new 7.5 F scopes, new bendable suction *ureteral access sheaths* (UASs), and new lasers with magnificent dusting abilities. Mini-PCNL is economically more feasible, without problems in cases of difficult retrograde access or need for prestenting; it requires fewer secondary procedures and guarantees much better flow that RIRS.

RIRS (Bogdan Geavlete)

Starting from the last place in the list of therapeutic approaches for renal calculi smaller than 2 cm in 2010, *retrograde intrarenal surgery* (RIRS) can actually compete with all the other current stone treatment practices. In 2023, the EAU Guidelines consecrated RIRS efficacy in treating stones up to 3 cm, depending on operator skills and frequently requiring staged procedures (2).

In comparison, despite the higher success rate in approaching lower pole calculi, *mini-percutaneous nephrolithotomy* (mini-PCNL) has been described as involving a higher rate of complications as well as a longer hospital stay (2).

The potential concern about the presence of residual fragments after the retrograde procedure proved to be clinically unjustified because more than four out of five cases of post-ureteroscopic renal stone fragments under 4 mm were found to either become stone-free due to spontaneous passage or retain asymptomatic stable-size fragments (7).

Aiming to reach an evidence-based comparison, a systematic review and meta-analysis including 18 eligible randomized-controlled clinical trials and involving over 1700 patients emphasized both mini-PCNL and RIRS as safe and effective alternatives in treating renal calculi of 1 to 3 cm. It also acknowledged the mini-perc capacity to provide a higher stone-clearance rate with a shorter operation time. On the other hand, the antegrade approach has been negatively characterized by significantly longer hospital stay, higher blood loss and transfusion rate, more severe complications, increased pain and higher hospital costs due to its invasive surgical profile (6).

Furthermore, a prospective cohort comparative study targeting precisely the current topic (average renal stone size of 15-16 mm) confirmed the few and not statistically significant differences between the two therapeutic alternatives. Mini-PCNL was described as the more cost-effective option, with the drawback of substantially longer hospital stay, while comparable sone-free rates were obtained after a single session (93% *versus* 89%) (8). It has been consistently underlined that RIRS provides similar therapeutic efficacy in comparison to mini-perc, according to statistically similar stone-free rate, together with reduced perioperative morbidity (shown by the diminished blood loss as well as the shorter recovery time), and despite the longer operative time (9).

At last, but not least, RIRS seems to benefit from therapeutic superiority over *extracorporeal shock-wave lithotripsy* (ESWL), in light of the literature data supporting the significantly higher stone-free rate and lower re-treatment rate, without an increase in the incidence of complications (10).

Finally, the choice for any alternative minimally-invasive stone treatment should largely rely on some decisive factors, such as stone location, kidney anatomy, associated comorbidities and patient's preference, as well as the urologist's expertise and the available medical equipment. Finally, it becomes increasingly clear that a patient-tailored therapeutic approach leads the way towards good clinical practice, while treatment algorithms and integrated management strategies are continuously evolving in the era of remarkable technological advances.

SWL (Christian Tuerk)

The 15 mm kidney stones have an indication for interventional stone removal and according to the EAU guidelines, both SWL and endourological procedures are available as the first choice for this purpose. In 2023, regularly updated systematic Cochrane reviews comparing SWL, ureteroscopy and percutaneous stone removal came to the conclusion that SWL may have lower three-month success rates but less complications compared to the alternatives (11). Another systematic review with network analysis, including 1674 patients, once more showed that SWL is the best option in terms of safety, although, at least for lower calyceal stones, the efficiency is worse (12). However, efficiency of SWL con be improved by proper patient selection and best practicing SWL-treatment. Factors for prediction of SWL-success are skin to stone distance, Hounsfield units with stone heterogeneity, stone size/volume (13), anatomy of collecting system, etc. In special situations SWL even could be the least burdensome way to treat depending on comorbidities, e.g. in patients with severe kyphoscoliosis including restrictive respiratory obstruction and anesthesia related difficulties (tracheal intubation). Best practicing SWL-treatment includes shock wave rate 1-1.5 Hz, ramping of SW-intensity, correct coupling, careful monitoring of both, stone targeting and patients movements during SWL (US), proper analgesia (limits movements and respiratory excursions) (14). Besides proper patient selection and best clinical practice post-SWL measures can improve outcome, like medical expulsive therapy or diuresis-inversion-percussion (15).

Providing proper patient and stone selection and with best clinical SWL-practice the 1.5 cm kidney stone is definitely a case for SWL with low invasiveness and few complications.

The 6 mm obstructing pelvi-ureteric junction (PUJ) stone

RIRS (Syed Jaffry)

Retrograde intrarenal surgery (RIRS) emerges as the optimal approach for managing a 6 mm *Pelvi-ureteric Junction* (PUJ) stone, despite the scarcity of data specific to this size. This methodology's support comes from indirect evidence and a comprehensive evaluation of various critical factors influencing treatment decisions.

Location plays a pivotal role in determining the approach for stone removal. A stone positioned at the PUJ presents unique challenges due to its proximity to the kidney and the potential for causing significant obstruction. RIRS, with its maneuverability and direct access capabilities, especially in cases with virgin ureters, either with or without the use of *Ureteral access sheaths* (UAS), offers a distinct advantage. It enables effective push-back techniques and complete stone clearance, even in the face of PUJ obstruction or a tortuous alpha loop in the proximal ureter.

The size of the stone, being 6 mm, resides in a grey zone where spontaneous passage is uncertain, thereby necessitating intervention. RIRS, with its ability to address stones of this size with minimal complications and favorable outcomes, stands out as a particularly suitable option.

Furthermore, the stone's composition, the presence and duration of obstruction, and whether the stone is impacted are all factors that RIRS can adeptly navigate.

RIRS also provides significant benefits in terms of patient safety and comfort. It eliminates the need to stop anticoagulation therapy, which is crucial for patients at risk of thromboembolic events. Additionally, for individuals with morbid obesity or body deformities, RIRS offers a safer alternative, reducing the risks associated with more invasive procedures.

Moreover, in anatomically challenging conditions such as horseshoe kidneys, RIRS demonstrates superior adaptability and effectiveness. While direct statistics for RIRS specifically targeting 6 mm PUJ stones are limited, the general success rate of RIRS for kidney stones supports the expectation of high *stone free rates* (SFRs) for such cases, adjusted for individual clinical scenarios. Thus, RIRS stands as the preferred method for managing 6 mm PUJ stones, balancing efficacy, safety, and patient outcomes.

Emergency SWL (eSWL) (Christian Tuerk)

In EAU-Guidelines shock wave lithotripsy is the first choice for interventional stone removal of up to 1 cm stones both, in the kidney pelvis and in ureter promising less invasiveness and complications but lower *stone free rates* (SFR) compared to endourological procedures. To address the current case of a 6 mm PUJ-stone the literature was examined with the question of the possible advantage of an early therapy.

Back in 2014 Sarica et al. showed in a retrospective case study that there is a highly significant relationship between ureteral wall thickness and the success rates of SWL (16). The ureter wall thickness is a sign of impaction and depends on time. A prospective randomized study comparing early (emergency) SWL with delayed treatment shows an impressive advantage of the eSWL over delayed SWL in both the SFR and the efficiency quotient after 1 day, 1 week, 1 month and 3 months (17). In 2023 a meta-analysis evaluating the efficacy of eSWL treating ureteral stones showed that SFR was statistically significant higher and faster in eSWL group with significant less auxiliary procedures (18). A matched-pair-analysis in 2021 from Switzerland compared immediate SWL vs delayed SWL after emergency stent insertion, including patient with PUJ-stones; e-SWL or stent respectively was performed within 48 hours after first presentation of patient; in this study once more SFR of 6-9 mm stones was significantly higher with lower reintervention rate compared to stent+delayed SWL (19).

In conclusion, the 6 mm obstructing PUJ-stone is definitely a case for emergency SWL showing low invasiveness, less complications and has much better results compared to delayed treatment, resulting in less loss of working days and being possible as an outdoor procedure depending on national health care.

Technical issues of urinary stone management

Patients on anticoagulants (Hichem Kouicem)

In chronic anticoagulant users undergoing surgery, bleeding and thromboembolism are common and serious complications.

There are two main classes of oral antithrombotic drugs: antiplatelet drugs (aspirin) and oral anticoagulants, including *vitamin K antagonists* (VKA) and *direct-acting oral anticoagulants* (DOAC) (Table 2).

The bleeding risk is associated with type of stone surgery and procedure as *extracorporeal shock wave lithotripsy*

Table 2.
Antithrombotic drugs.

Anticoagulants agents	Vitamin K antagonists (VKA)	Warfarin
	Direct-acting oral anticoagulants (DOAC)	Direct thrombin inhibitors Dabigatran
		Direct Xa inhibitors Apixiban Endoxaban Rivaroxaban
	Indirect thrombin inhibitors	LMWH UHF Fondaparinux
Antiplatelet agents	COX inhibitors	Aspirin
	ADP inhibitors	Clopidogrel Prasugrel Ticagrelor
	Glycoprotein IIb/IIIb inhibitors	

(ESWL), *percutaneous nephrolithotomy* (PCNL), and open surgery.

In case of low bleeding risk, the evidence suggests that VKA might not be stopped.

Urgently needed surgery must take place under full antiplatelet therapy despite the increased bleeding risk.

For high thrombotic risk, VKA must be stopped 5 days before surgery with bridging using full-dose of > *low-molecular-weight heparin* (LMWH) or *unfractionated heparin* (UFH) started 3 days before surgery. LMWH or UFH will be stopped respectively one day and 4 to 6 hours before surgery. VKA will be resumed 12 to 24 hours after the procedure. For urologists, surgery performed on a patient under anticoagulant treatment led to manage the Risk-Risk Balance between bleeding and thromboembolism (20).

Antibiotic resistance (Adam Halinski)

UTIs are becoming increasingly difficult to treat owing to the rapid spread of drug resistance among Gram-negative organisms. UTIs are at the forefront of the antibiotic resistance problem because 9% of all antibiotic prescriptions in the ambulatory setting in the USA are done for the treatment of UTI. The problem is related to broad-spectrum antibiotics that have been the drug of choice to treat both community- and hospital-associated UTIs.

The increase of antibiotic resistance and appearance of *multi-drug resistant* (MDR) pathogens in the course of UTI is related to high rates of inadequate antibiotic empirical therapies prescribed without the antibiotic susceptibility testing and finally resulting in an ineffective UTI treatment.

The risks of multi-drug resistant pathogens are: recurrent UTIs (21), hospitalization, age, genitourinary disturbances, prior use of antibiotics (22, 23), increased use of broad-spectrum antibiotics leading to increased antimicrobial resistance and multi-resistance of bacteria (24).

Health care practitioners should be educated on the suitability of urine culture and should read the literature to compare it with local resistance rates. Rapid molecular tests could shorten the waiting time for urine culture. Development of new antibiotics and probiotics can decrease the resistant rate. On the other hand, antibiotic-sparing therapeutics including small-molecular inhibitors of bacterial adhesion, immunomodulatory therapy that alters the host response to infection and vaccinations against microbial targets could also be helpful.

In conclusions, pre-interventional urine culture is mandatory. Antibiotic therapy is important in the UTI treatment but in recent years it is becoming more challenging due to increasing resistance to routinely applied antibiotics. The use of an intrarenal urine culture and stone culture is recommended to adapt antibiotic therapy in case of postoperative infectious complications.

Zero radiation ultrasound guided PCNL
(Mohammed Alameedee)

PCNL is wide world used operation to remove renal stones , fluoroscopy is used as a guidance for PCNL, but it is limited by the risk of radiation, so ultrasound-guided PCNL is an option to replace fluoroscopic guidance avoiding the limitation of X-ray exposure. It has multiple advantages with respect to fluoroscopic guidance as no radiation, imaging of structures between skin and kidney to assess depth of the access needle and prevent organ injury , no need for contrast media (especially in case of failure of retrograde pyelogram due to difficult ureteric catheterization), safety in pediatric and pregnant patients, feasibility in supine position with no need for lithotomy position and ureter stent fixation, and cost-effectiveness. On the other hand, ultrasound guided PCNL is challenging to the surgeon because it needs good eye hand coordination with long training curve and because it can be difficult when perinephric fat make the identification of access needle tip difficult by ultrasound, especially in obese patients. Hydro dissection can be used to overcome these difficulties by injection of normal saline through the access needle along the tract from skin to target calyx to dissect muscle layers and fatty tissue by saline which leads to easy identification of needle. Optical hydro dissection allows easy identification of the access needle with concomitant continuous optical control by use of a 2 mm telescopic lens incorporated into an access needle associated with pressured saline infusion which dissect tissue layers along tract from skin to target calyx.

Ultrasound-guided PCNL is an option to replace fluoroscopic guidance avoiding the limitation of X-ray exposure. It has also multiple advantages as imaging of neighboring organs, no need for contrast media and ureteral catheterization safety in pediatric and pregnant patients and cost-effectiveness. Optical hydrodissection by use of a 2 mm telescopic lens incorporated into an access needle allows easy identification of the needle with concomitant continuous optical control.

Tubeless PCNL (Elenko Popov)

In the last decades, *percutaneous nephrolithotomy* (PCNL) experienced enormous technical advancements like miniaturization of the available armamentarium (2). To further decrease the invasiveness of this procedure, safety and efficacy of different exit strategies like the tubeless PCNL technique have been explored. The presence of nephrostomy tube has several advantages potentially lowering complications rate as maintaining renal drainage, allowing for re-intervention if needed; avoiding urine extravasation; and preventing continuous bleeding by compressing the dilatation tract. Conversely, it also has significant drawbacks: prolonging hospitalization; increasing postoperative pain score and analgesic requirements; not being so suitable for ambulatory/day-case surgery.

A significant problem in comparing use of nephrostomy after PCNL with tubeless PCNL in the literature is the standardization of nomenclature! Series can be different depending on type of PCNL (standard, mini, super-mini, micro, nano), characteristics of patients and stones, and types of nephrostomy (tube, small-bore tube, tubeless, not so tubeless, almost tubeless, totally tubeless). However, all meta-analyses comparing standard and tubeless PCNL reach similar conclusions (25-28): the key to effective outcome with tubeless PCNL is appropriate patient select, tubeless procedures are considered safe and effective in low-risk patients, most of reported studies conclude that a tubeless procedure is associated with less patient discomfort and shorter hospital stay compared to the standard PCNL, the complication rate, including postoperative fever, haematocrit decrease, stone-free rate and urine extravasation usually did not differ between the different exit strategies.

However, all of them report a risk of bias due to high heterogeneity of results.

In conclusion, tubeless PCNL has several advantages and is relatively safe, but it may involve great risks if the patients are not carefully selected. Therefore, the indications should be strictly controlled, and the technical requirements are relatively high. The tubeless PCNL must also be implemented by experienced surgeons.

Choice of Laser for Lithotripsy (Elenko Popov)

The development of laser technologies is one of the main prerequisites in modern endourology. Massive breakthroughs were achieved in the last years by second generation Holmium-YAG, Thullium fibre laser, pulsed Thulium laser (29-31).

The ideal laser for lithotripsy should be effective, safe, multitasking, fast, noiseless, ergonomic, and cost-effective.

New Ho:YAG technologies as high power, high frequency and pulsed modulations have shown promising results for lithotripsy by reducing retropulsion with good ablation efficiency. High peak power makes it particularly good for percutaneous nephrolithotomy. High intrarenal temperatures and choice of correct setting are still concerning points. *Thulium fiber laser* (TFL) has arrived to be one of the main players in flexible ureteroscopy. Being highly efficient and quick, and by producing micro-dusting the laser is quickly heading to become a gold standard. The new pulsed Thulium YAG is the newest laser. For now, only in-vitro studies show promising results with efficient lithotripsy. As the peak power lies between Ho:YAG and TFL it may be able to adequately perform when needing high and low power lithotripsy.

Pressure and temperature during RIRS (Syed Jaffry)

The review of temperature and pressure measurements during *Retrograde intrarenal surgery* (RIRS) highlights crucial insights and challenges inherent to the procedure. These measurements are vital for ensuring patient safety and optimizing surgical outcomes, yet they present specific difficulties that demand a careful and informed approach. The challenges associated with accurately measuring and interpreting temperature and pressure levels during RIRS can significantly impact the procedure's efficacy and the patient's postoperative recovery. Recognizing these challenges is the first step towards mitigating potential risks and enhancing the overall success of the surgery.

To address these issues effectively, it is essential to focus on refining measurement techniques and developing novel methods for data analysis. This includes improving the precision of intraoperative measurements and exploring advanced approaches for interpreting this data in real-time. Moreover, establishing a clear correlation between these intraoperative metrics and long-term patient outcomes is crucial for validating the effectiveness of RIRS procedures.

Collaboration between urologists, engineers, and data scientists is critical for advancing this field. Together, they can work towards creating integrated systems that facilitate the seamless collection, analysis, and visualization of crucial surgical data. Such systems would not only improve the accuracy of temperature and pressure measurements but also enhance the decision-making process during RIRS.

In the interim, adherence to current practices such as the use of *Ureteral access sheaths* (UAS) with or without suction devices, continuous fluid management monitoring, and the emphasis on surgeon skill development remain pivotal. These practices, alongside the optimal duration of surgery and a personalized approach to patient selection and procedure planning, are essential for maintaining the standard of care in RIRS. Future research should thus prioritize these areas to ensure continued improvement in patient care and surgical outcomes in the realm of urology (32).

Urinary stent technology (Federico Soria)

The three pillars of stent improvement are the development of new biomaterials, new coatings, and new stent designs. Furthermore, the development of drug eluting stents is a topic on which many research groups are working.

About the coatings, the aim is to prevent the formation of biofilm, which is associated with asymptomatic bacteriuria and urinary tract infection, as well as the encrustation of stents. One fact researchers must be aware of is the severe antimicrobial resistance surveillance in Europe policy.

The aim is to coat stents with substances that prevent the adhesion of bacteria and crystals on their surface. To this end, different strategies have been developed, the most promising being the development of antimicrobial peptides with bactericidal capacity (33).

The great innovation in ureteral stents is mainly the development of research lines about drug-eluting stents. The main idea in this topic is that the stents, in addition to improving urinary drainage and scaffolding, can perform other functions such as local drug delivery. This could be in the near future with different applications. There are experimental studies on drug-eluting stents releasing *Rapamycin*, *Paclitaxel* or *Pirfenidone* to inhibit relapse of ureteral strictures after endoureterotomy, in relation to inhibition of the mTOR pathway or reduction of TGF expression which inhibits collagen deposition (34, 35). In this regard, our research group developed a new coated mitomycin-eluting biodegradable ureteral stent for intracavitary instillation as an adjuvant therapy in upper urothelial carcinoma (36). Thus, the development of drug-eluting stents is the near future, aiming to reduce the adverse effects of stents and to topical drug delivery to avoid systemic drug administration, thereby reducing complications.

Bioresorbable stents (Federico Soria)

Unfortunately, the ideal ureteral stent has not yet been designed. Nevertheless, several authors have outlined its characteristics very well, one of the features is related to ease of insertion and removal. Obviously, the answer to easy removal is not having to remove them, which means that they would be biodegradable.

The characteristics of an ideal *biodegradable ureteral stent* (BUS) should be: excellent biocompatibility; moderate mechanical properties; complete degradation without obstructive fragments; prevent migration; good flexibility for stent placement; radiopacity; visibility on ultrasound; controlled degradation rate; no mutagenic, antigenic, and carcinogenic activity; no degradation with toxic metabolites (37).

About the current limitations to BUS development, there are some main points to improve.

Degradation rate control: one of the most important factors in BUS development is the ability to control the degradation rate in order to develop a stent that will have the required duration.

Biomechanical properties control: the balance between degradation and scaffold is very difficult to achieve.

Fragmentation size control and non-obstructive fragments release: this is another essential requirement and has been the reason why the first BUS designs were not successful, as the degradation of the stents was often obstructive. New designs, have managed to overcome this drawback thanks to the use of polymers and copolymers with different degradation rates.

There are different research groups working on BUS. Our research group has been developing a BUS for the last few years. BraidStent is a braided stent made of synthetic polymers and copolymers that are degradable by hydrolysis. This allows the suitable degradation rate, without obstructing fragments and the adjustment of degradation according to the needs of the individual patient (38, 39).

To summarize, it is certainly not a fiction. Researchers have greatly improved BUSs and preclinical studies have already yielded very positive results. In my opinion, the glass is half full and getting fuller.

Complications of surgical stone treatment

Complications of PCNL (Hammad Ather)

Of the three minimally invasive surgical options (*Shock wave lithotripsy/SWL, flexible ureteroscopy/fURS and percutaneous nephrolithotomy/PCNL*), in the management of urolithiasis, PCNL is considered as the most invasive although it has high efficacy particularly for intermediate and large stones including staghorn calculi.

In a review paper, *Seitz et al.* (40) indicated that although no deviation from the normal postoperative course (Clavien 0) was observed in 76.7%, the rest had complications of various grades including death in 0.04%. The two major most common complications include septic complications and bleeding. Fever, and sepsis were observed in 11 and 0.5% respectively. The bleeding related complications with need for transfusion and embolization were observed in 7 and 0.4% respectively. Authors observed a wide variation in reporting of these complications in the absence of a specific tool for reporting procedure specific morbidity. Clavien system is widely used to report urological complications, however, procedure specific scoring is more desirable. In a paper published by de la *Rosette et al.* (41). Authors observed that Clavien classification demonstrates high validity although inter-rater reliability is low for minor complications.

Abdominal organ injury including colonic, splenic, liver, gall bladder and bowel injuries are fortunately quite rare but are associated with significant morbidity. In a systematic review *Ozturk et al.* (42) reported 51 colonic injuries out of 13000 patients undergoing both supine and prone PCNL. All gall bladder injuries necessitated cholecystectomy, whereas liver injuries were mostly amenable to conservative treatment. Laparotomy and diversion are rarely performed for colonic injuries, particularly in the absence of signs of peritonitis. Major bleeding complications are managed by embolization.

In conclusion, PCNL related major complications are not frequent but significant. Improvement in technique, equipment and better understanding have improved the outcome. There is a downward trend in the incidence, but also most of the complications are managed conservatively.

Management of PCNL complications (Alberto Budia Alba)

PCNL is a minimally invasive surgical technique, but it is not free of complications. The reported complication rate is approximately 23.7% (40). Although the most frequent is fever (10.8%), serious complications can occur such as pleural lesions (1.5%), sepsis (0.5%), organ injury (0.4%) and even death (0.05%).

Perhaps, the best way to avoid them is to try to prevent them. Adequate planning of the caliceal approach depending on the patient's position, adequate bridging treatment of anticoagulated or anti-aggregated patients, and preoperative cultures that allow the patient to arrive at surgery with sterile urine are effective measures to reduce the probability of complications.

The complications of this technique are divided into intraoperative and postoperative. Intraoperative complications can be prevented by accurate access through the calyceal papilla and performing delicate maneuvers in the dilation of the tract, which reduces intraoperative bleeding. The use of a safety guide allows, in the event of failure to reach the urinary system, a new access using the safety guide without the need to re-puncture. In case of perforation of the urinary tract during dilation, if the perforation is small, treatment can be completed, but if the leak is significant, it should be postponed after insertion of an urinary diversion. The hydrothorax should be managed with pleural drainage; colon perforation, if it is intraperitoneal, requires surgical repair and, if it is extraperitoneal, it can be managed conservatively with urinary and retroperitoneal drainage.

The most feared postoperative complication is urinary sepsis, more frequent in insulin-dependent patients, women and in case of large and infective lithiasis (43). An early identification and treatment is the key to a good therapeutic response.

The second most serious postoperative complication is late hemorrhage, secondary to a pseusoaneurysm or arteriovenous fistula, which in most cases requires angioembolization.

Therefore, although PCNL is a minimally invasive technique, it is not free of complications, some of them potentially serious, which should be identified early and treated properly.

Complications of URS (Juan Pablo Caballero)

Ureteroscopy (URS) is a technique with a low frequency of severe complications (44, 45). But some complications can cause real nightmares. We must emphasize the importance of complications generated by ureteral catheters. Never place ureteral stents unnecessarily after ureteroscopy.

We can identify URS-related complications until more than 6 months later. Some of those that, due to their severity, we must avoid and know how to treat are those dependent on high pressure in the urinary tract, sepsis of urinary origin, renal bleeding, and those secondary to applying excessive force to the urinary tract, as ureteral avulsion and ureteral stricture.

Sepsis occurs more frequently in patients with a positive preoperative urine culture. Therefore correct prophylaxis, or treatment, guided by the antibiogram and knowledge of local antibiotic resistances is mandatory. Sepsis will occur more frequently if we exceed intrapelvic pressure levels greater than 30 mmHg.

High pressure can also lead to bleeding from the renal parenchyma that will cause flank pain and a drop in hemoglobin levels. Treatment will usually be by selective embolization of the renal parenchyma.

One of the most devastating complications is ureteral avulsion, which can be proximal and/or distal (46, 47). Thinner or less compliant ureters are more sensitive to these complications, especially if we use larger caliber ureteroscopes. Urgent surgical repair by laparoscopy is essential.

Ureteral stricture can occur up to 7 months after the intervention. It requires a high degree of suspicion after ureteral injuries or impacted stones. For its diagnosis we need imaging and functional tests, such as the isotopic renogram.

ECIRS: indications and complications (Luis Llanes)

Endoscopic combined intrarenal surgery (ECIRS) combines retrograde and antegrade approaches using both flexible and rigid endoscopes for treating large or complex renal stones (48).

It was first described by *Gaspar Ibarluzea* in 2007 (49) and after, *Cesare Scoffone* created the acronym ECIRS (endoscopic combined intrarenal surgery) in 2008.

The indications of ECIRS can be summarised in two (48):

1. To treat staghorn or complex kidney stones and limit the number of percutaneous accesses.
2. To treat simultaneous multiple kidney and ureteral stones or an impacted pelvic stone.

The modified supine position by Galdakao is the most extended patient position to do an ECIRS because two simultaneous surgeons are working and helping each other with total access to the urinary tract.

Complications can potentially occur in the procedure: during access, procedure or exit process, and can be classified according to the modified Satava classification system (50):

- Grade 1: an error without consequences
- Grade 2a: an error was identified and corrected immediately with endoscopic surgery intraoperatively
- Grade 2b: a complication treated with endoscopic surgery in another operative session.
- Grade 3: a complication that requires open or laparoscopic surgery

The postoperative complications of ECIRS, according to the Clavien-Dindo classification, are the same as in *percutaneous nephrolithotomy* (PCNL): haemorrhagic, infectious, obstructive, splanchnic injuries, infundibulum stenosis, surgical material retained and renocutaneous fistula. Different meta-analyses and systematic reviews comparing ECIRS with PCNL for large and complex kidney stones show that overall complications, severe complications, postoperative fever, haemoglobin decrease, transfusion rate and Clavien Dindo complications are always in favour of ECIRS (51, 52).

Diagnostic work-up

Genetic testing (Giovanni Gambaro)

Genetic testing in nephrolithiasis patients consents the diagnosis of known genetic conditions causing stones and previously unknown gene causing renal stones.

Many of the monogenetic diseases thus identified can develop CKD/end-stage renal disease and/or metabolic bone disease. In this case, the genetic diagnosis has prognostic implications and is helpful for the prevention of nephropathy and osteopathy. Few monogenic diseases identifiable with genetic testing also have specific therapies for personalized/precision therapy. This is the case of primary hyperoxalurias, 1.25-(OH) D-24 hydroxylase deficiency- infantile hypercalcemia. In the future, other therapies may be able to cure some other genetic defects causing nephrolithiasis. Their identification is essential.

However, we should ask ourselves whether all nephrolithiasis patients should undergo genetic testing.

In studies in which genetic testing was systematically carried out to diagnose Mendelian diseases causing nephrolithiasis, the most frequent diagnosis was cystinuria. This is a diagnosis that can be made much more quickly and at much lower costs with the analysis of the morphology and composition of the stone, with the dosage of urinary cystine, with the observation of typical crystals in the urinary sediment, and finally, during a procedure of laser lithotripsy with the typical odor that emanates.

Frequent genetic diagnoses can also be formulated based on specific easily determined laboratory test patterns (e.g., distal renal tubular acidosis).

On the other hand, for the majority of monogenic diseases causing nephrolithiasis, there are no specific therapies.

Another point to consider is that the prevalence of genetic nephrolithiasis in adult nephrolithiasis patients is lower than reported. If cystinuria, APRT deficiency, and xanthinuria are excluded from the series in which genetic tests have been performed, a maximum of 4% of nephrolithiasis patients in tertiary reference centers are affected (53-55). If we move from the super-selected case series of tertiary reference centers to the general population of adult stone patients, less than 1% of them are carriers of genetic mutations other than cystinuria (56).

The success in identifying cases of genetic nephrolithiasis is the direct consequence of selecting cases with clinical characteristics that make one suspect its existence (Table 3) (57). It is in these adults that it is reasonable to per-

Table 3.

Warning elements on a possible genetic origin of nephrolithiasis.

Early onset
Family cases
Consanguineous parents
Highly-active stone disease (bilateral, multiple stones, frequently recurrent)
Associated nephrocalcinosis
Renal hyperechogenicity
Tubular dysfunction and related manifestations (statural growth deficit, polyuria, bone disorders)
Renal failure
Extrarenal manifestations (sensorineural hearing defects, ocular abnormalities, neurological disorders)
Particular stone composition and crystalluria (whewellite, cystine, dihydroxyadenine, xanthine)

form genetic testing. Since childhood age is one of the main elements for suspecting genetic stones, it is rational to carry out genetic tests in all children.

Stone analysis (Alberto Trinchieri)

According to EAU guidelines (2), after stone passage a reliable stone analysis by infrared spectroscopy or X-ray diffraction is mandatory. AUA guidelines (58) confirmed that, when a stone is available, a stone analysis should be obtained at least once. A consensus conference (59) pointed out that infrared spectroscopy or X-ray diffraction to identify mineral types should be preceded by examination of the stone under a stereomicroscope to assess which part (or parts) of the stone should be taken for molecular analysis.

Visual identification of stone morphology requires a skilled observer, therefore development of methods for evaluation of stone morphology are highly desirable.

Examination of whole stones provides insight into how the stone has formed and grown, which is partly lost when examining a few fragments extracted from the urinary tract after lithotripsy.

Unfortunately, in real-life some stone centers still perform the chemical examination of the stone and not all laboratories that perform the spectroscopic examination fulfill the quality requirements (60).

The analysis of digital images of stones by deep convolutional neural networks could allow the classification of stones based on their color and texture. This technique can be used in the laboratory for the analysis of photographs of stones or fragments extracted from the urinary tract, but above all for the classification of stones during endoscopic examination in the operating room.

Stone examination allows the diagnosis of rare stones such as cystine, dihydroxyadenine and xanthine stones; the diagnosis of stones with specific etiology such as uric acid, sodium or ammonium urate, struvite and brushite stones; the differentiation of subtypes of calcium stones (calcium oxalate monohydrate, calcium oxalate dihydrate and carbapatite); to provide information on the components of mixed stones.

Stereoscopic microscopy (petroscopy) or the analysis of digital imaging allows the identification of subtypes of calcium oxalate or calcium phosphate stones with morphology associated with a specific etiology such as primary hyperoxaluria (COM 1c), enteric hyperoxaluria (COM 1e), renal tubular acidosis (Carbapatite type IV a2), struvite (type IV c) and brushite (type IV d) (61).

Endourological stone observation (Elenko Popov)

The analysis of the stone is a crucial step of the work up of renal stone forming patients as it provides relevant information on the pathogenic mechanisms of renal stone formation. The analysis of the stone can be performed only after the spontaneous expulsion of the stone or its fragments or after its surgical removal. Many efforts have been made to develop imaging modalities able to reliably diagnose in-vivo the physico-chemical composition of the stone before the procedure of stone removal.

The increasing efficiency of lasers in "*dusting*" and "*popcorning*" modes and the improved performance of endoscopic devices led to smaller stone fragments, which reduce the accuracy of the stone analysis (microscopic morphology and infrared spectroscopy) by the lack of components representativeness considering that 48.6% of the stones have a mixed composition (62). Moreover, *Keller et al.* (63) recently showed the impact of laser-based dusting on changes in stone composition with significant changes in the infrared spectra (particularly for weddellite, carbapatite, struvite, and brushite).

Consequently, examination by infrared spectroscopy of the stone powder by itself could not provide sufficient information of stone composition.

This finding reinforces the need to observe the morphology of the stone before laser-induced destruction to preserve an etiological approach. The examination should includ a visual observation of the stone surface first, before laser fragmentation, then visual observation of the section and the nucleus after laser stone section. Endoscopic stone observation is feasible but necessitates significant experience, specific expertise, and training. Even in in these optimal conditions the rate of concordance of endoscopic examination and microscopy is 80-90% for whewellite (Ia or Ib = 85%, Id = 92%, n = 12; Ie = 80%), 85% for weddellite (IIa or IIb = 85%), 91% for uric acid (IIIa or IIIb), 50% for carbapatite-struvite association (IVb), and 65% for brushite (IVd) (64).

The results of a multi-center expert setting (65), more resembling the real-world scenario, including 32 clinicians from 9 different countries, with significant expertise shows overall accuracy 39% (250 out of 640 predictions), with calcium oxalate dihydrate stones correctly detected in 69.8%, calcium oxalate monohydrate in 41.8%, uric acid in 33.3%, calcium oxalate/uric acid in 34.3%, cystine in 78.1%. Precision rates for struvite (15.6%), calcium phosphate (0%) and mixed calcium oxalate/calcium phosphate (9.3%) were quite low.

There is a significant tendency for improvement in endoscopic stone recognition in the future: advances in endoscope technology, such as Raman spectroscopy, polarization endoscopy and hyperspectral imaging; advances in digital technologies; potential implementation of *artificial intelligence* (AI) technologies for automated endoscopic stone recognition. On the other hand, problems still need to be solved as bias in generating datasets, mathematical methods weaknesses, mixed stones, and significant difference between *ex-vivo* and *in-vivo*.

In conclusion, the information that can currently be obtained from endoscopic observation of the stone is limited, as even expert surgeons may not be able to reliably predict the composition of the stone. However, the imminent future technological innovations should allow an accurate prediction of the composition of the stone in its different components, thus adding information to that obtainable with the post-op analysis of the fragments after lithotripsy.

For this reason, it should be emphasized the importance of an accurate description of the stone in the report of the endoscopic procedure that should be always accompanied with a photograph or video clip of the stone. Urology residents should receive a specific training on the macroscopic aspect of urinary stones and should be encouraged in endoscopic recognition of the most frequent types of renal stones.

Desktop scanning electron microscopy for urinary stones (A. Costa-Bauzá)

Scanning electron microscopy (SEM) is a non-destructive technique that in the backscattered electron mode provides information about the three-dimensional structure of surface or sections of a kidney stone and a very clear characterization of crystals morphology.

The methodology currently used for SEM consists of placing the stone on a sample holder, with no need to cover with gold. After observation, the sample is in the same state as before SEM analysis. Furthermore, SEM can be used with auxiliary techniques, especially X-ray scattering analysis *energy dispersive spectrometry (EDS)*. This provides reliable data on the elemental composition of a specific point or a general area of a stone (66-68). A substance present in minute quantities, even at trace level, that is not detectable by IR spectroscopy can be identified. Currently EDS can detect C, N and O, important elements for uric acid and ammonium urate identification.

Thus, SEM-EDS can provide information about the:

- morphology of crystals in the stone allowing their unequivocal identification
- internal structure with location of crystalline phases and minor components
- identity of the initial area of calculus formation
- changes in the crystalline shape or composition.

Currently, many renal calculi are fragmented prior to analysis, which implies a partial loss of information. However, with stereoscopical microscopy, several representative fragments can be selected, and then use SEM-EDS to provide additional information for determining stone etiology.

Therefore, together with stereoscopical microscopy and IR spectroscopy, SEM-EDS is a fundamental tool for the study of kidney stones, and the information it provides has great clinical and practical importance. SEM will be used more in the future due to the development of desktop models that are easy to use, more affordable, and provide results with the same quality as larger and more expensive models.

Urinary and intestinal microbioma (Juan A. Galán-Llopis)

Oxalobacter formigenes that has been largely studied in relation to its role in degrading oxalate and referred to as the main link between gut´s microbiome and urinary stone disease. However, not every species of *Oxalobacter* are related to stone disease and the latest studies suggest that the entire *gut microbiome* (GMB) seems to be involved in the pathophysiology of urolithiasis, and can have different roles supported by the presence of some short chain fatty acids, that will protect gut´s epithelium, also having an anti-inflammatory effect. GMB dysbiosis exists in the kidney stone forming patients (more bacteroides, *E. Coli* and *shigella*, less prevotella-9) and in order to restore this microbiome and prevent kidney stone formation, several measures including rational use of antibiotics, probiotic preparations and adjusted diet, and fecal microbial transplantation can be accomplished (69-72).

Urine is not sterile and some microorganisms, the urobiome, different in stone formers and healthy individuals, can be detected by the combination of metagenomic analysis using *Next generation sequencing* (NGS) techniques (*Amplicon, Shotgun*) and the *enhanced quantitative urine culture* (EQUC) protocol (73). Differences between the stone and urine microbiota have been described, and that may indicate that certain bacteria contribute to urinary stone disease pathophysiology. The microbiota of upper tract and bladder urine are similar, but there are differences between stone and urine microbiota, with a significant decrease of microbiota diversity in stone formers. Urobiome can be regulated by pro and prebiotics, diet, and with immunomodulators. Consensus will allow for proper future studies on urobiome research.

Urinary pH (Juan A. Galán-Llopis)

Urinary pH in humans shows a circadian rhythm and can be affected by different situations including diet, drugs, stress, gender, and genetic and metabolic diseases. Apart from the balance between urinary stone promoters and inhibitors, both the time that the urine is within the urinary tract, and the urine pH are needed to form a stone. A high urine pH (> 6.2), independent of diet, and hypocitraturia are the most important risk factors for calcium phosphate stones, especially in women (74). Fasting urine pH > 5.8 non-responding to acidification, associated to hypercalciuria, hypocitraturia, and the presence of apatite or brushite stones should direct suspicion to incomplete distal *renal tubular acidosis* (RTA) (75). Low urine pH (< 5.5), low urine volume and high *uric acid* (UA) osmolality will lead to UA stone formation (76). Cystine is highly soluble at urine pH higher than 7.5. The only stones that seem independent of urine pH are papillary *calcium oxalate monohydrate* (COM) and 2.8 dihydroxyadenine. Urine pH should be properly measured with laboratory pH meters, preferably within two hours of collection and after 12 hours fasting, or else with a digital pH meter (Lit-Control) several times a day (fasting, and after meals) (77). A correct pH measurement will allow to treat and monitor the patient with prophylactic alkalizing drugs (potassium citrate, sodium bicarbonate) and/or preventing uric acid stone formation or increasing its dissolution with theobromine (78), and/or decreasing uric acid in urine with allopurinol/febuxostat. Urine acidification can be achieved by using L-methionine and or ammonium chloride. Phytate is the correct choice for kidney stones prevention whenever pH is neutral.

24 Hour urine analysis (Dirk Kok)

Twenty-four hour urine analysis has a place during patient intake and during follow-up.

Analysis of crystalluria can reveal the stone type which helps choosing preventive treatment and determining which urine parameters are relevant to monitor.

For stones that are formed due to excessive crystal formation inside the nephron followed by plug formation (cystine, xanthine, uric acid, slightly soluble drugs, hyperoxaluria related calcium oxalate) the presence of the specific crystal type and the size of the crystals tell if the renal conditions in the patient are inducive of stone formation or not (79).

Treatment will be aimed at maintaining a low excretion rate for the stone components and at maintaining urine pH in a range where the solubility of the specific compound is high. Urine analysis should comprise those factors.

Most stones will consist of calcium oxalates and/ or calcium phosphates. For these stones the relevant urine parameters are calcium, oxalate, phosphate, citrate, magnesium and pH. These should be measured at patient intake, after stone removal and at the start of treatment.

Treatment will consist of medication (e.g. alkali), drinking advice and lifestyle advice (80). Dietary advice includes avoidance of high oxalate content foods and balanced intake of protein (acid load) and fruit/vegetables (alkali load) (81). Urine pH and citrate content give information on the acid/base balance and the risk of forming calcium oxalate aggregates (82).

Finally, all stone formers will benefit from a drinking advice. Monitoring urine volume always makes sense for all patients.

Of course, the big catch in this is patient compliance (83). It is difficult to follow lifestyle advice especially when your problem of stone formation started decades earlier and everything at present appears to be normal (84). For this large group of patients, the most sensible manner of follow up will be to provide means for measuring urine volume (actual measurement of looking at the color) and measuring urine pH at home.

Urinary Supersaturation Revisited:
A proposal for a simpler indicator of stone risk (Allen Rodgers)

Despite shortcomings, urinary *supersaturation* (SS) is the most comprehensive of the numerous physicochemical risk factors employed in urolithiasis research (85). SS for *calcium oxalate* (CaOx) stones depends on the concentrations of free unbound *calcium* [Ca2+] and *oxalate* [Ox2-] species. These species in turn depend on the speciation and pH of the urine solution itself. As such, pH is correctly considered as an indirect measure of SS and a crucial indicator of stone risk. Indeed, a commercially available meter for home use is available for measuring urinary pH in stone patients undergoing therapy (86). Urinary pH levels which should be targeted by the patients for reducing the risk of CaOx, calcium phosphate and uric acid crystallization are provided. Given that lowering SS of CaOx is a strategic goal in the administration of therapeutic and prophylactic preparations, it is instructive to revisit the physicochemical aspects of this important urinary property and to recognize the aforementioned primary influencers of stone risk [Ca2+] and [Ox2-]. Of these, the latter has been shown to be the limiting factor in CaOx crystal formation in urine (87). As such, stone formation is much more sensitive to changes in [Ox2-] than [Ca2+].

Unfortunately, measurement of [Ox2-] cannot be routinely achieved. Measurement of [Ca2+] is also difficult but easier. It is proposed that the manufacturers of the pH-measuring device for home use consider incorporating a Ca-ion sensitive electrode into their current design to allow patients to monitor urinary pH and [Ca2+] simultaneously, notwithstanding that the factors are not independent.

This will provide a double-check of risk leading to a more comprehensive assessment of treatment efficacy and risk of stone recurrence.

Are there clinical applications of macromolecular stone promoters and inhibitors? (Allen Rodgers)

A major challenge for researchers investigating the possible role of *urinary macromolecules* (UMMs) as promoters or inhibitors of kidney stone formation is that many of these molecules play both roles depending on the chemical composition and properties of the urine in which they are operating (88, 89). Well known examples include Tamm-Horsfall protein which has been shown to promote and inhibit *calcium oxalate* (CaOx) aggregation depending on its degree of desialylation and osteopontin which in its phosphorylated form inhibits CaOx nucleation and aggregation (in different CaOx hydrates) but promotes aggregation in its phosphorylated -deficient form. Besides acting on crystallization processes per se, urinary macromolecules also are able to influence crystal-cell and crystal-crystal attachment processes, each one of which can modulate aspects of the stone formation process.

Their activity depends on urine environment and the nature of crystal and cell surfaces. Additionally, presence and absence of chemical, structural and conformational defects, increased or decreased expression, and the difficulty of finding consistent reproducible results from various experimental models exacerbate the challenge. Given this myriad of factors which requires untangling and characterization, it seems unlikely that methods for controlling them by optimizing some and minimizing others is imminent. At this stage, it is suggested that there are no realistic clinical applications of urinary macromolecules in stone management or prophylaxis.

Nephrolithiasis as a systemic disorder (Bernhard Hess)

There is increasing evidence that many renal stone formers (SF) exhibit ‘non-urologic’ systemic metabolic abnormalities such as *metabolic syndrome* (MS), cardiovascular disease or bone disease. A disease is defined as systemic if several organs/tissues or the whole body are affected (90). We analyzed additional anthropometric/metabolic data obtained from 531 non-selected consecutively referred renal stone formers, originally investigated for the prevalence of *incomplete distal renal tubular acidosis* (idRTA) (75).

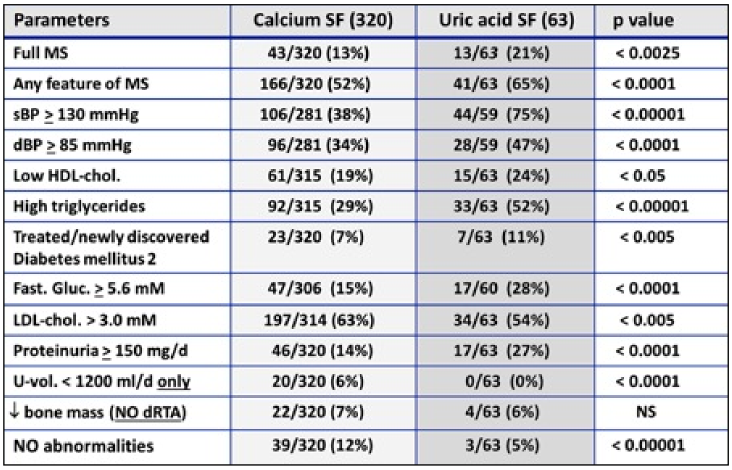
Among them, 139 were primarily classified as having systemic disease: 8 cystine stone patients, 66 calcium stone formers with various secondary causes (bariatric surgery, primary hyperparathyroidism, inflammatory bowel disease, medullary sponge kidney, treatment with carboanhydrase inhibitors or HIV medication, glomerular disease) and 65 calcium stone formers with idRTA.

The remaining 392 SF (320 idiopathic calcium, 63 uric acid, 9 infection SF) were screened for the following markers of systemic disease: 1) full MS or 2) traits thereof, 3) LDL-cholesterol > 3.0 mmol/l and 4) proteinuria > 150 mg/d as marker of cardiovascular risk, 5) very low urine volume < 1.2 L/d, likely due to reduced thirst sensitivity, and 6) low bone mass without idRTA.

Only 3/63 (5%) of uric acid SF (UA-SF) were without any marker of systemic disease, compared with 39/320 (12%) of idiopathic calcium SF (ICSF), $p < 0.0001$.

Among infection SF, only 1 out of 9 was without systemic markers.

Table 4.
Markers of systemic diseases in idiopathic calcium vs uric acid stone formers.



Parameters	Calcium SF (320)	Uric acid SF (63)	p value
Full MS	43/320 (13%)	13/63 (21%)	< 0.0025
Any feature of MS	166/320 (52%)	41/63 (65%)	< 0.0001
sBP ≥ 130 mmHg	106/281 (38%)	44/59 (75%)	< 0.00001
dBP ≥ 85 mmHg	96/281 (34%)	28/59 (47%)	< 0.0001
Low HDL-chol.	61/315 (19%)	15/63 (24%)	< 0.05
High triglycerides	92/315 (29%)	33/63 (52%)	< 0.00001
Treated/newly discovered Diabetes mellitus 2	23/320 (7%)	7/63 (11%)	< 0.005
Fast. Gluc. ≥ 5.6 mM	47/306 (15%)	17/60 (28%)	< 0.0001
LDL-chol. > 3.0 mM	197/314 (63%)	34/63 (54%)	< 0.005
Proteinuria ≥ 150 mg/d	46/320 (14%)	17/63 (27%)	< 0.0001
U-vol. < 1200 ml/d only	20/320 (6%)	0/63 (0%)	< 0.0001
↓ bone mass (NO dRTA)	22/320 (7%)	4/63 (6%)	NS
NO abnormalities	39/320 (12%)	3/63 (5%)	< 0.00001

A direct comparison of Idiopathic calcium vs. uric acid stone formers is depicted in Table 4.

Two or more systemic markers of systemic disease were more often present in UA-SF (49/63, 78%) than in ICSF (183/320, 57%), p < 0.0001. Overall, only 43 of 531 non-selected SF (8.1%) were without markers of systemic disease.

The following conclusions can be drawn: 1) Nephrolithiasis should be considered a systemic disease, as 92% of SF exhibit markers of systemic disease. 2) Recurrent CaSF and UA-SF should primarily be referred to internists or nephrologists for evaluation not only of urine chemistries, but systemic pathologies such as MS or traits thereof, elevated LDL-C, overt proteinuria, hyperparathyroidism, incomplete dRTA, bone disease, medullary sponge kidney, inflammatory bowel disease, bariatric surgery and lithogenic drugs.

Screening of high-risk stone formers (Alberto Trinchieri)

Some renal stone formers are considered "*high-risk*" due to the high tendency to relapse with a consequent increased risk of obstructive episodes and surgeries which can cause a damage of renal function.

In general, non-calcium stones have the greatest tendency to recur, although some subgroups of calcium stones also have high recurrence as calcium stones associated with some genetic diseases (hereditary hypercalciurias, hereditary distal tubular acidosis, primary hyperoxaluria) or acquired diseases (primary hyperparathyroidism, sarcoidosis, distal tubular acidosis secondary to autoimmune diseases, immobilization syndrome and other bone diseases, therapy with carbonic anhydrase inhibitors, enteric hyperoxalurias associated with ileal resection, chronic inflammatory bowel disease and some types of bariatric surgery).

High-risk renal stone formers need early diagnosis to start specific treatments. Stone analysis allows the identification of most non-calcium stones: infection stones (struvite), uric acid and urates, cystine and other rare stones (dihydroxyadenine, xanthine).

Most forms of calcium stones secondary to specific acquired diseases can be diagnosed by a thorough history associated with biochemical tests for the evaluation of calcium phosphate metabolism and measurement of fasting urinary pH.

Some forms of stones are secondary to monogenic hereditary defects which can be diagnosed by searching for mutations in a large panel of candidate genes (91) (Table 5).

The study of this panel of genes (or similar panels) allowed the diagnosis of a monogenic hereditary defect in 16.8-30% of pediatric series with nephrolithiasis. In a large pediatric series with a very low average age of 2.5 years, a monogenic defect was demonstrated in 39% (92). Conversely, in adult populations the rate of monogenic hereditary defects does not exceed 7%, including genetic defects associated with cystinuria which are relatively frequent (92). On the other hand, the cost of these investigations still represents a limiting factor in their routine use, although there has been a significant decline in costs with *next-generation sequencing* (NGS) approaches.

For this reason, it has been suggested that intensive research into genetic etiology should be reserved for children who form kidney stones before 5 years of age, especially if coexisting nephrocalcinosis and/or consanguinity are present. For children > 5 years and adults, the genetic study must be preceded by a careful assessment of the phenotype to select cases in which a genetic defect is suspected (93).

The study of the phenotype is of particular importance for the diagnosis of cystinuria and primary hyperoxaluria.

Early diagnosis of cystinuria is mandatory due to the relative frequency of the disease (1/7000 newborns) and of cystine stones (approximately 6-8% in pediatric series, 1% in adults). Cystinuria is caused by mutations of SLC3A1 and SLC7A9 genes encoding for the two subunits of the transporter of cysteine, ornithine, lysine and arginine in the proximal tubule which cause elevated urinary excretion of cystine. The phenotype of these patients is potentially easy to identify through stone analysis, the use of a colorimetric test in urine (which is limited by the toxicity of one of the reagents), the demonstration of typical crystalluria and ion chromatography (for diagnostic confirmation). However, in real life the diagnosis of cystinuria is still delayed compared to the first

Table 5.
Panel of candidate genes related to nephrolithiasis.

Calcium metabolism	ADCY10, ALPL, ATP6V0A4, ATP6V1B1, CA2 , CASR, CLCN5, CLCNKB, CLDN16, CLDN19, CYP24A1, FAM20A, HNF4A, KCNJ1, MAGED2, OCRL, SLC12A1, SLC4A1, VDR
Hypercalciurias and Renal Tubular Acidosis	ATP6V0A4, ATP6V1B1, SLC4A1
Defects in renal phosphate tubular reabsorption	SLC34A1, SLC34A3, SLC9A3R1
Hereditary hyperuricosurias	HPRT1, SLC22A12, SLC2A9
Primary hyperoxaluria	AGXT, GRHPR, HOGA1, SLC26A1
Cystinuria	SLC3A1, SLC7A9
Other metabolic stone diseases	APRT, XDH
Orher candidates genes for association with nephrolithiasis	AMMECR1, AP2S1, CLDN10, GDNF, GNA11, OXGR1, SLC13A5, SLC26A6, SLC26A7, SLC7A13, TRPV5, TRPV6

episode of stones and the percentage of patients with renal failure is high despite the availability of effective pharmacological treatments (94). Greater organization and attention from clinicians should therefore be required for the diagnosis of this disease, especially when the onset occurs after the age of 16. An interesting option could be post-natal screening which seems to be justified by the prevalence of the disease and the availability of effective therapy. Post-natal diagnosis has been tested in some communities in Spain where the disease has been diagnosed in 1/4129 newborns (95) and cystine stones were observed in 10.5% of cases after a 17 years follow up (96).

Colon hyperechogenicity at prenatal ultrasound examination has been reported in some patients who presented with cystinuria and could be used to select newborns to screen for the genetic defect (97).

Primary hyperoxaluria is the result of 3 rare genetic defects of hepatic oxalate metabolism which cause an exaggerated excretion of oxalate in the urine. An effective therapy for the treatment of primary hyperoxaluria type I (lumasiran) has recently been introduced (98).

The phenotype is not always easily identifiable as it is associated with the formation of calcium oxalate monohydrate stones with the same chemical composition as idiopathic calcium oxalate stones.

Diagnosis is easier in cases with early and severe presentation with nephrocalcinosis, renal failure and manifestations of systemic oxalosis. In cases with onset in adulthood and without nephrocalcinosis the diagnosis is often delayed after 5 years from initial presentation and at end stage renal disease (in 30-60% of cases) (99).

The recognition of the phenotype is usually based on the measurement of 24-hour oxaluria which is not always easily accessible and can be cumbersome for pre-analytical reasons of sample collection and preservation.

These problems could be overcome with the development and diffusion of rapid qualitative diagnostic tests for the recognition of oxaluria which have already been described in numerous reports (100).

Alternatively, the greater diffusion of stereoscopic microscopy for the analysis of stones, in addition to infrared spectroscopy or X-ray diffractometry, could help to recognize the pathognomonic morphology of calcium oxalate monohydrate stones of patients with primary hyperoxaluria which present different color and structure with respect to idiopathic COM stones (101).

Prevention strategies

Personalized medicine (Giovanni Gambaro)

Personalized or precision medicine is not only aimed at specific molecular targets of that specific patient. We have examples of such medicine in the treatment of nephrolithiasis. This is the case of Thiopronine for cystinuria, of Rifampin in Infantile Hypercalcemia CYP24A1 gene mutation, and finally of Lumasiran and Nedosiran in primary Hyperoxalurias. However, the meaning of precision or personalized medicine is much broader. These terms mean a prevention and treatment approach considering individual genetic variations and environmental and lifestyle conditions. It is a concept that those involved in the prevention of nephrolithiasis know well. The EAU guidelines have well interpreted the concept of personalized medicine when they state that the individual risk of recurrence and systemic complications of stones must be assessed globally because this is imperative for pharmacological treatment (14).

No antithesis exists between personalized medicine and public health interventions to prevent stones. The first addresses a small part of stone patients with a high risk of recurrence and systemic complications, which must be identified among the more numerous subjects who form one or a few stones during their entire lifespan. Just to give an example (please consider that the following percentages are approximate and for illustrative purposes only), let's assume that the prevalence of nephrolithiasis in the general population is 10%; only 10% of these could be genuinely recurrent stone patients. Among these, only 10% might have secondary forms. Well, personalized treatment should only be reserved for these last two categories of subjects.

The AUA and EAU guidelines suggest a selective approach to pharmacological prevention and recommend conducting a metabolic study on the 24-hour urine of stone patients (14, 59). Unfortunately, although this is only part of the overall risk assessment of a stone patient, the metabolic study is often ignored in clinical practice (102, 103). However, there is an antithesis between personalized medicine and an empirical approach to preventing nephrolithiasis. The empiric approach (104), including lifestyle, nutritional, and pharmacological measures administered to stone patients, is based solely on stone composition with minimal or no metabolic urinary investigations. This exposes the renal stone patients to a risk of under-diagnosis and under-treatment, i.e., missing the chance to properly diagnose and treat that minority of those with nephrolithiasis who could benefit from specific and/or ancillary treatments (e.g., parathyroidectomy or treatments for slowing the progression of chronic kidney disease), the inherited and secondary forms. Furthermore, other problems with such an approach are unwanted adverse events and un-loyalty of patients (105).

In a nephrolithiasis patient, a complete diagnostic work-up should be carried out with the aim of:

- Identification of secondary forms of nephrolithiasis
- Diagnosis of idiopathic calcium nephrolithiasis
- Risk assessment of chronic kidney disease and metabolic bone disease
- Identification of patients who need to be treated to prevent stones and systemic complications (6).

At the end of the work-up, only a minority of patients will need a personalized treatment.

The risk of considering nephrolithiasis only as a problem of public health policies is that this is interpreted as a renunciation of the commitment to identify the few patients who, on the contrary, require personalized therapies.

Public Health Policy (Alberto Trinchieri)

In the last three decades, the prevalence of kidney stones has increased worldwide. Higher prevalence rates are observed in developed countries although increase of prevalence rates are also expected in developed countries (106). The increase in the prevalence of kidney stones is linked to the greater impact of environmental risk factors (diet, lifestyle, climate), while the impact of genetic factors remains unchanged. In particular, the role of climate factors is increasing because of global warming and urbanization which exaggerates the effect of increasing global surface temperatures (urban heat islands) (107, 108). The increase in the prevalence of kidney stones is associated with the change in the clinical presentation of the disease and in the spectrum of stone composition due to the increased impact of environmental factors compared to genetic factors. The comparison of case series studied in the same country in different periods of time demonstrates that the average age of patients with urinary stones has increased over the last 30 years from the 5th to the 6th decade (109). The spectrum of stone composition also changed during this period. The frequency of infection stones (struvite) has decreased in most geographical areas thanks to the improvement of social and health conditions. Furthermore, a trend towards a reduction in calcium phosphate stones in favor of an increase in the frequency of calcium oxalate was observed. In the context of calcium oxalate stones, an increase in the frequency of calcium oxalate monohydrate stones and a reduction in calcium oxalate dihydrate stones was also observed. In some southern areas of Western countries (*Texas, Southern Europe*) an increase in the frequency of uric acid-containing stones has been observed, while this trend has not been observed in more northern geographical areas. The frequency of uric acid-containing stones tends to be positively correlated with the increase in environmental temperature.

Furthermore, the prevalence of hypercalciuria, the urinary saturation values with respect to calcium oxalate, calcium phosphate and uric acid have progressively reduced over time. Finally, the average interval between the first episode of stone disease and subsequent episodes of recurrent stone disease tends to lengthen (110, 111).

The "*new*" presentation of urinary stone disease is characterized by higher renal stone prevalence, higher age at stone onset, longer interval between stone episodes, more frequent calcium oxalate monohydrate and/or uric acid stones, less frequent hypercalciuria, and lower urinary saturation.

At present, renal stone prevalence is higher but most renal stone formers present a mild to moderate disease with late onset of stone formation. This trend is mostly related to a change of environmental risk factors for atone formation.

This trend cannot be countered only by increasing the provision (and costs) of curative services.

On the contrary, measures of primary prevention are highly needed (general practitioners, media, social media). In fact, patients who form the first stone at middle-age or after need a simplified screening including clinical history, stone analysis, measure of calcium/phosphate metabolism, urinary pH, and urine culture. They usually only require general measures such as high fluid intake, diet and alkalinization.

Furthermore, lifestyle adaptation to climate change is also requested at institutional level (landscape, urban and building strategies to augment adaptive capacity to hot weather) and at individual level.

Personalized medicine or public health policy? (Dirk Kok)

The answer to this question depends on the process by which the stone was formed: fixed or free particle mechanism (112).

Both require supersaturation of the surrounding fluid, being urine inside the nephron, urine in the urinary tract or interstitial fluid.

Personalized medicine can prevent stones that start inside the nephron or in the urinary tract.

An example is infection stones that are formed from high concentrations of calcium, magnesium, phosphate and ammonium and a high pH. Effective prevention requires removal of all stone fragments (resident bacteria), supplying the correct antibiotics and drugs that reduces urine pH and urease activity. You need to be aware that a negative urine culture does not exclude the presence of urease producing bacteria, because they may reside inside crystal material or urothelial cells (113).

Similarly, we also know how to prevent stones that start by crystallization in the nephron because of high blood values plus local nephron conditions. For instance, drugs of which supersaturation increases at high pH may form crystals in the loop of Henle. This can be detected by looking for drug crystals in the urine (114, 115). When the numbers of crystals formed become too high, aggregates may block the duct of Bellini and start stone formation. For such drugs it should be remembered that there exists a window of plasma levels with a lower limit determined by the desired effectivity and a higher limit determined by the crystallization risk. It might be wise to monitor crystalluria for any new drug in order to detect future risks of stone formation. Cystine, xanthine and uric acid stones are other stone types that start from high plasma values and abnormal urine conditions. Limitation of the excretion of metabolites in combination with steering urine pH in the appropriate direction plus, if possible, adding compounds that bind the stone forming material will prevent new stone formation and examining crystalluria has a good monitoring function.

For some of stones made of calcium oxalate and phosphate salts where high plasma values are involved (genetic hyperoxaluria, hyperparathyroidism, extreme intake of oxalate or oxalate precursors) the same principles as described above can be maintained.

On the contrary, the problem lies with the calcium stones that are related to lifestyle and may start with renal plaques. The whole process can take up to decades (116). Here prevention involves long term adaptation of the stone former to a lifestyle that poses less of a stone forming risk. This is a very difficult task that requires a combination of personal attention by the doctor and public health or commercial initiatives that aim to direct people towards a healthier lifestyle (117-119). Someone who is forming the first stone can only be helped by the latter two.

Future research

Artificial Intelligence (AI) -
A window to the future (Alberto Trinchieri)

Artificial intelligence is a branch of computer science that develops systems capable of performing tasks that would require human intelligence such as learning, reasoning, problem solving, perception and understanding language. Artificial intelligence is expressed through various technologies such as machine learning, expert systems, natural language processing, computer vision and robotics.

In particular, machine learning consists of the development of algorithms to make predictions or decisions based on patterns identified in the analyzed data without explicit programming. A subset of machine learning is deep learning through algorithms organized in complex layered neural networks that are exercised by analyzing unstructured or unlabeled data.

Artificial intelligence is used in medicine with various applications for the purpose of collecting medical history through voice or text analysis to create real-time transcriptions of the conversation between physician and patient, detection of clinical signs, automated image analysis, classification, and categorization of pathological, radiological, and endoscopic images.

The applications of artificial intelligence in the management of the renal stone patients have several purposes: automated identification of ureteral stones on CT imaging, prediction of stone composition by clinical parameters, prediction of 24-hour urinary risk factors by demographics and clinical parameters, and assessment of stone composition by evaluation of images (photographs, endoscopic videos) (120).

The analysis of digital photographs or endoscopic intraoperative views by deep *convolutional neural networks* (CNNs) can allow the identification and classification of kidney stones.

A recent meta-analysis has shown that in the last 5 years the predictive positive value has increased for different types of stones from 50-75% to 96-99% (121).

An application for smartphones equipped with a miniaturized microscope was also developed which demonstrated an accuracy of 88% (122).

Artificial intelligence techniques have also been used for the prediction of postprocedural outcomes such as the prediction of spontaneous passage of ureteral stones, the stone-free status after SWL, the lower pole stone clearance after SWL, the stone growth after SWL, the prediction of success after PCNL.

In conclusion, the extensive application of artificial intelligence in Urology will revolutionize the decision-making process. Efficiency, accuracy and precision will be enhanced with decreased workload for clinicians.

Synergy between urologists, nephrologists and scientists in basic stone research (Kyriaki Stamatelou)

Urology is currently the dominant specialty involved in the management of kidney stones. Depending on the particular setting of care and the individual referral practices, the role of Nephrologists in urolithiasis is usually limited. Nephrologists are generally involved in the medical management of kidney stones only when repeated recurrences or a noticeable kidney injury or kidney failure occur. In recent years collaboration between Basic Research scientists and urologists and nephrologists happens in very few places in the world, mainly kidney stone clinics, academic research centers and centres of excellence for urolithiasis (123-125).

Yet, it is apparent that basic scientists, including biochemists, geneticists, and physiologists, can contribute to our understanding of the fundamental mechanisms of kidney stone formation uncovering molecular pathways, genetic factors, and physiological processes that are involved in stone development but remain incomprehensible.

Synergy between clinical practitioners and basic scientists can extend to translational research, where findings from basic science are translated into clinical applications and help develop targeted therapies and preventive strategies based on the latest scientific insights. Synergy in clinical trials is also essential for evaluating new surgical techniques, medical treatments, or preventive strategies.

Synergy can also include the formation of Interdisciplinary Teams that would address all aspects of disease management including acute stone events, recurrences, co-morbidities, preventive measures and patient education.

An excellent example of contemporary meaningful synergy is the development of a revolutionary drug for the treatment of Primary Hyperoxaluria Type 1. The application of a biotechnology breakthrough, small RNA interference molecules for silencing a gene coding a protein, that stops the production of oxalate and alleviates the symptoms of the catastrophic disease.

In conclusion, the synergy between urologists, nephrologists, and scientists in basic kidney stone research enhances the depth and breadth of investigations, leading to a more comprehensive understanding of kidney stone formation, risk factors, and treatment options. This collaboration is essential for developing effective strategies to prevent kidney stones and improve the overall care of affected individuals.

CONCLUSIONS

(Athanasios Papatsoris)

Urolithiasis is a multifactorial disease, increasing in prevalence worldwide. At the same time, minimally invasive treatment techniques are under constant evolution, changing the landscape of optimal management. The present article aimed in covering all aspects in diagnosis and management of urolithiasis, using high-quality, evidence-based material, in order to help urologists tailoring the stone disease management. Given the continuous improvement in all aspects of endourology, future studies are needed to provide urologists with updated material in treatment incorporating individual patient preferences along with surgical expertise.

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of the event who remembered him several times. The program was inspired by his scientific philosophy in particular the collaboration between urologists, nephrologists and scientists in basic stone research and the creation of relationships between experts from both, developed as well as developing countries. Noor died on 13 February 2024 two weeks after his last successful meeting.
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