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ARTICLE

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Rational evaluation of urinary stone disease

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Abstract This article outlines the recent state of the art in the metabolic diagnosis of stone disease. The current literature in the field of urolithiasis—including the existing German and EAU-Guidelines as well as the Conference Book of the 1st International Consultation on Stone Disease—was critically reviewed. As far as possible the references were rated according to the EBM criteria. The occurrence of stone disease in the western world is increasing greatly. Modern lifestyle, dietary habits and excess weight—problems of affluent societies—are emerging as the important promoters of the "stone boom" in the new millennium. This even affects children, whose stone prevalence is otherwise significantly less than that of adults. Criteria for the high-risk group of stone formers were clearly defined. A diagnostic standard is formulated for the basic and the elaborate metabolic evaluation of a stone patient. The diagnostic pathways for the most important stone types and metabolic disorders, respectively, are described. The present concept allows a precise risk classification of each stone former and facilitates the decision whether stone-specific measures in addition to the basic metaphylaxis are recommendable or not.

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Background

Worldwide epidemiological data show an increase in prevalence and incidence rates of stone disease. In Germany, for instance, the incidence rate rose during the last decade from 0.54% to 1.47% [1]. In the United States, an increase in stone disease of 37% was observed over the last 20 years [2]. The reasons are multifold: lifestyle, dietary habits and improved medical care. Today, excellent options for interventional stone therapy, such as ESWL, URS and PCNL, warrant a comfortable stone management. The new methods are non- or minimally-invasive; they can be performed often without general anesthesia in an outpatient setting; only some procedures require a short hospital stay. It is, therefore, not surprising that stone removal has become more attractive than elaborate metaphylactic measures. In the daily routine, metabolic evaluation and metaphylaxis—which comprises metabolic therapy and secondary prevention of stone disease—have regrettably become less important. On the other hand, we have learnt from a lot of other diseases that prevention is superior to intervention. And, in times of financial pressure, it is more cost effective.

The consensus concept considered the EAU-Guidelines [3], the results of the 1st International Consultation on Stone Disease (Paris, 2001) and the current literature since 2000. It is at present the most comprehensive and updated review in this field.

Our aim was to compile a concept which is applicable in any clinic or practice. To optimize the acceptance of the recommended diagnostic pathways in the daily routine, a compact programme was defined which warrants a high quality standard with a minimum of measures. Deliberately, such procedures or therapies were excluded which represent the expertise of only a few highly specialized stone centers.

Patient selection

Not every patient that passed a stone needs elaborate metaphylactic treatment. More than 50% of all recurrent stone formers have just one recurrence during their lives [4]. In these patients, general drinking and nutritional advice is sufficient. If stone disease is highly recurrent and troublesome, specific measures and pharmacological therapy are justified, likewise in patients at high risk (Table 1). About 10% of the recurrent stone formers have more than three recurrences. It can be estimated that 15–24% of all stone patients require specific metabolic measures for recurrence prevention [1, 5]. Consequently, it is of particular importance to define the risk of stone recurrence in each patient as early as possible.

Table 1 Patients at high risk for recurrent stone disease

Highly recurrent stone formation (≥3 stones in 3 years)
Infection stones
Uric acid and urate stones (gout)
Children and teenagers
Genetic determined stones
• Cystinuria
• Primary hyperoxaluria
• RTA type I
• 2,8-Dihydroxyadenine
• Xanthine
• Cystic fibrosis
Brushite stones
Hyperparathyroidism
Gastrointestinal diseases (Crohn's disease, malabsorption, colitis)
Solitary kidney
Residual stone fragments (3 months after stone therapy)
Nephrocalcinosis
Bilateral vast stone burden
Family history for stone disease

Consented clinical pathway—diagnostic programme

The decision whether a patient needs elaborate metabolic evaluation or not can be facilitated by following the sketched algorithm in Fig. 1. After stone passage the patient should be assigned to the low risk or high risk group of stone formers. *Stone analysis* by infrared spectroscopy or X-ray diffraction is an indispensable prerequisite for the correct classification of the patient. Today, stone analysis is a mandatory examination in each stone patient. As a next step, the *basic evaluation programme* as scheduled in Table 2 should be performed to find out severe metabolic risk factors.

Combining the results of the stone analysis and the basic evaluation programme it is possible to detect the high risk stone formers (see Table 1). Only this exactly defined group of patients needs further workup: the *elaborate metabolic evaluation programme*. The recommended diagnostic pathways in the *elaborate metabolic evaluation programme* are stone specific and more complex. This first orientation about the possible causes of stone formation allows classifying any stone patient as low risk or high risk with regard to stone recurrence.

Stone analysis

Stone composition gives information about the potential metabolic disorders behind the "symptom" stone. Thus,

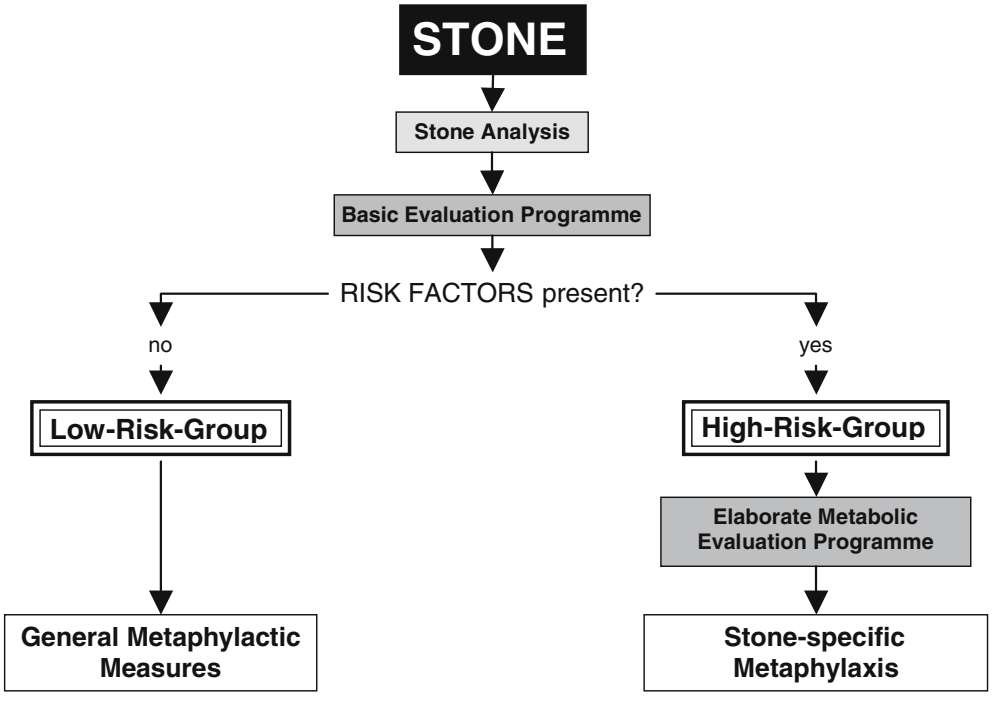

Fig. 1 Current concept (scheme) of the appropriate pathway in metabolic diagnostic and metaphylaxis of stone disease for a patient who passed a stone. If one or more of the risk factors listed in Table 1 is present, elaborate metabolic evaluation should be considered

Table 2 The basic evaluation programme for stone formers

Medical history	Stone history (former stone events, family history) Dietary habits Medication chart
Clinical workup	Physical examination Ultrasound
Blood analysis	Creatinine Calcium (ionized calcium or total calcium + albumin) Uric acid
Urinalysis	Dipstick test: leucocytes, erythrocytes, nitrite, protein, urine-pH, specific weight Urine culture

it is indispensable to collect the calculi that the patient passed in order to find out the stone components. Generally accepted standard methods in stone analysis are *X-ray diffraction* and *infrared spectroscopy*. Both methods are precise enough to detect stone components in the range of 5–10%. If available, *polarization microscopy* would be the third reliable method, but de facto it is performed with expertise only in a few stone centers [6–10, 11].

Basic evaluation programme

The basic evaluation programme is a minimum of laboratory investigations to detect severe disorders related with stone formation. Table 2 specifies the programme in detail. Exact *medical history* is the first step to discover patients at risk (Table 1) [12]. Then the *clinical workup* shows, e.g., if the patient is stone-free or not or if his or her urinary tract is obstructed. *Blood analysis* should detect patients with severe metabolic and organic disorders like renal insufficiency, hyperparathyroidism or other hypercalcaemic states and hyperuricaemia. *Urinalysis* at that time will be performed routinely with a dipstick test for demonstration of red cells, white cells and bacteria (nitrite), and for information on the pH level and specific weight of the urine. In case of signs of infection, urine culture is required.

Elaborate metabolic evaluation programme

Analytical preconditions

For the analytical workup, the collection of two 24 h urine samples is the recommended standard, despite other collecting regimes proposed in the literature. The collecting bottles should be either prepared with 5% thymol in isopropanol (10 ml for a 2 l bottle) or stored at a temperature of 8°C or less. Immediate urinalysis after the completion of collection is recommended to minimize the potential error [8, 13].

Table 3 Specific evaluation programme for calcium oxalate stone formers

Basic evaluation programmme +	
Blood analysis	Parathyroid hormone (in case of increased calcium levels) Sodium Potassium Chloride
Urinalysis	Urine-pH profile (measurement after each voiding, minimum four times a day) 24 h urine sample—two collections • Volume • Urine-pH • Specific weight • Calcium • Oxalate • Uric acid • Citrate • Magnesium

Calcium oxalate stones (Table 3)

In case of elevated levels of ionized calcium (or total calcium and albumin) intact parathyroid hormone may confirm the suspected hyperparathyroidism. Constantly acidic values (< pH 6) in the urine pH profile indicate an "acidic arrest" which may promote the co-crystallization of uric acid. Constant non-acidic urine (pH > 5.8) in the day profile is a sign of renal tubular acidosis so far as urinary tract infection is excluded. The diagnosis of renal tubular acidosis is established with the ammonium chloride loading test. Absorptive hyperoxaluria should be evaluated with the ^{13}C-oxalate absorption test [8, 14–17].

Calcium phosphate stones

Hyperparathyroidism, renal tubular acidosis and urinary tract infections must be considered as the possible etiology of calcium phosphate stones. Although both minerals contain calcium and phosphate carbonate apatite and brushite are two totally different stone types. Carbonate apatite crystallization occurs at pH levels ≥6.8; it may be infection associated or form mixed calculi with calcium oxalate. Brushite, however, crystallizes in more acidic and stable urine (optimum pH 6.5–7.2) at high calcium and phosphate concentrations without any relation to urinary tract infections.

Infection stones (Table 4)

Urinary calculi related with infection are: struvite, carbonate apatite and ammonium urate. Urine culture

Table 4 Specific evaluation programme for infection stone formers

Basic evaluation programme + Urinalysis	Urine-pH profile (measurement after each voiding, minimum four times a day)

typically shows infection with urease producing bacteria; the most important ones are specified in Table 5. The urease reaction releases bicarbonate and ammonium leading to an alkaline urine pH and facilitating magnesium ammonium phosphate crystallization.

Nephrocalcinosis (Table 6)

The causes of nephrocalcinosis are various. Main etiological risk factors are hyperparathyroidism, disorders in vitamin D metabolism and renal tubular acidosis.

Uric acid and urate stones

Constantly acidic values (< pH 6) in the urine pH profile indicate an "acidic arrest" which promotes the crystallization of uric acid. Hyperuricosuria is the second etiological factor of these stones. Abnormal uric acid excretion occurs in the case of dietary excess, endogenous overproduction or catabolic states of the organism. Hyperuricaemia may be present, but is not necessarily associated with stone formation. In contrast to uric acid, ammonium urate calculi form in alkaline urine (pH > 6.5). Ammonium urate stones are related with urinary tract infection, malabsorption and malnutrition.

Table 5 The most important urease producing bacteria

Enterobacter aerogenes
Haemophilus influenzae
Klebsiella
Proteus mirabilis and Proteus vulgaris
Providencia
Pseudomonas
Serratia
Staphylococcus aureus
Ureoplasma urealyticum

Table 6 Specific evaluation programme in patients with nephrocalcinosis

Basic evaluation programme	
+	
Blood analysis	Parathyroid hormone (in case of increased calcium levels)
	Vitamin D and metabolites
	Sodium
	Potassium
	Chloride
	Blood gas analysis
Urinalysis	Urine-pH profile (measurement after each voiding, minimum four times a day)
	24 h urine sample—two collections
	• Volume
	• Urine-pH
	• Specific weight
	• Calcium
	• Phosphate
	• Oxalate
	• Uric acid
	• Citrate
	• Magnesium

2,8-Dihydroyadenine stones and xanthine stones

Both stone types are rare.

2,8-Dihydroxyadenine A genetically determined defect of the adenine phosphoribosyl transferase (APRT) causes a high excretion of poorly soluble 2,8-dihydroxyadenine in urine [18, 19].

Xanthine An autosomal-recessive hereditary defect of the enzyme xanthine oxidase (XO) causes extremely high xanthine concentrations in urine, while the levels of serum uric acid are typically low. The only therapeutic options are urine dilution and a diet with reduced purine content [8, 20].

Cystine stones

A genetically determined transport defect for dibasic amino acids leads to an increased excretion of the poorly soluble cystine in urine. Cystine solubility depends strongly on urine pH: at pH 6.0 the limit of solubility amounts to 1.33 mmol/l. In cystinuric patients the daily excretion exceeds 0.8 mmol/day [6, 8].

Stones with unknown composition

An exact *medical history* is the first step to discover risk factors (Table 1). The *diagnostic imaging* begins with the ultrasound examination of both kidneys to clarify whether the patient is stone-free. If stones are sonographically present, an unenhanced spiral CT should follow in order to differentiate between calcium containing and non-calcium calculi based on Hounsfield unit determination. *Blood analysis* should detect patients with severe metabolic and organic disorders like renal insufficiency, hyperparathyroidism or other hypercalcaemic states and hyperuricaemia. *Urinalysis* will be performed routinely with a dipstick test as described above. If there are signs of infection, urine culture is required. Constantly acidic pH values (< pH 6) in the profile indicate an "acidic arrest" which may promote the crystallization of uric acid. Constant non-acidic urine (pH > 5.8) in the day profile is a sign of a renal tubular acidosis provided that urinary tract infection is excluded.

Conclusion

With each urinary stone it should be borne in mind that the event is only the symptom of a disorder. Thus, removal of the stone remains a symptomatic therapeutic approach. Diagnostic evaluation in accordance with the

guidelines involves little time or effort if the system is adhered to. Taking into account the results of the stone analysis and the basic evaluation, ''high-risk'' patients can be determined quickly and easily. The additional metabolic clarification will provide important hints for an efficient metaphylaxis subsequently.

Excellent diagnostic tools are available to determine the causes of urinary stone disease, but we are lagging badly in their application for routine diagnosis.

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