Eur J Pediatr (2014) 173:353–359
DOI 10.1007/s00431-013-2165-6

ORIGINAL ARTICLE

# Demographic characteristics and metabolic risk factors in Croatian children with urolithiasis

**Danko Milošević · Danica Batinić · Daniel Turudić · Danko Batinić · Marija Topalović-Grković · Ivan Pavao Gradiški**

Received: 10 July 2013 / Revised: 27 August 2013 / Accepted: 22 September 2013 / Published online: 6 October 2013


**Abstract** The aim of this study was to assess demographic data, clinical presentation, metabolic features, and treatment in 76 children with urolithiasis presented from 2002 to 2011. Urolithiasis is responsible for 2.5/1,000 pediatric hospitalizations, with new cases diagnosed in 1.1/1,000 admissions. From the observed period, two-fold rise of incidence rate was observed. Compiling the data from other pediatric institutions in our country, we estimated present overall incidence rate in Croatia as 6.5/100,000 children under 18 years. There were 41 boys and 35 girls (ratio 1.17:1). The mean age at diagnosis was 9.7 (range 0.8–16) years and follow-up duration was 5.3 (range 1.8–10) years. Renal colic (75.0 %) and hematuria (57.89 %) were the main symptoms. In 65.78 % of children, stones were unilateral. Stones were located in kidney in 52.63 %, in the ureter in 26.32 %, and in bladder in 6.58 % cases. Stone analysis showed calcium oxalate in 75.0 % of the cases. Associated urinary tract abnormalities were found in 19.73 % children. Most common metabolic disturbances were hypercalciuria (47.37 %) and idiopathic or mild hyperoxaluria (18.42 %). Urine saturation (EQUIL2) was elevated in 61.84 % cases. Spontaneous stone evacuation occurred in 51.21 % children. Extracorporeal shock wave lithotripsy, surgical evacuation, and endoscopic removal of calculi were performed in 21.0, 6.58, and 5.26 % of cases, respectively. Follow-up conservative therapy, consisting of fluid/diet recommendations and additional potassium citrate and/or chlorothiazide in children with increased risk, was sufficient for stone recurrence prevention in 92.1 % of children. In *conclusion*, the study gave insight in epidemiology and metabolic disturbances of urinary stone disease in Croatian children.

**Keywords** Urolithiasis · Children · Metabolic risk factors · Therapy

D. Milošević (✉) · D. Batinić · D. Batinić
University Children's Hospital, University of Zagreb School of Medicine and Clinical Hospital Center Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia
e-mail: danko.milosevic@zg.t-com.hr

M. Topalović-Grković
University Clinic for Anesthesiology and Intensive Care, University of Zagreb School of Medicine and Clinical Hospital Center Zagreb, Zagreb, Croatia

D. Turudić · I. P. Gradiški
University Children's Hospital, University of Zagreb School of Medicine, Kišpatićeva 12, 10000 Zagreb, Croatia

## Introduction

Urinary stone disease is not rare in children. Recent epidemiological studies reveal its increasing incidence during the last century in Western countries [10, 26, 28, 32, 35–37, 45]. Demographic factors and metabolic disturbances underlying urinary stone disease are continuously monitored in numerous countries. Previous research of urinary stones in Croatia was published a decade go with main emphasis on epidemiology [7]. Since metabolic disorders are proven to be the major causes of urinary stones in many countries, we decided to concentrate not only to demographic and clinical characteristics in our patients with urolithiasis but also to enrich the previous report from our country with full metabolic risk factors investigation.

## Patients and methods

We retrospectively reviewed medical records of 76 children with urinary stone disease from various parts of Croatia referred to our Nephrology Department for assessment, who were followed up between 2002 and 2011. Medical records were reviewed for gender, age, follow-up duration, family history, clinical symptoms, location and composition of

stones, urinary metabolic risk factors, presence of urinary tract abnormalities, and treatment results.

The stones were documented through plain abdominal X-ray and/or ultrasound, and in selected cases, by intravenous urography, in all except seven children, in whom imaging was negative due to known previous spontaneous stone evacuation. Voiding cystourethrography was performed in children with recurrent urinary tract infections and/or hydronephrosis on renal ultrasound in order to determine the vesicoureteral reflux. Additional clinical/laboratory examination was performed in order to confirm specific conditions in some of the patients, such as distal tubular acidosis, caudal regression syndrome, and oculocerebrorenal syndrome.

In all children including infants and toddlers, urinary stone metabolic risk factors were evaluated. Hypercalciuria was defined as urinary calcium excretion >0.1 mmol/kg/24 h, primary hyperoxaluria as urinary oxalate excretion >1 mmol/1.73 $m^2$/24 h with glycolate excretion >0.50 mmol/1.73 $m^2$/24 h or L-glyceric acid excretion >5 μmol/l, idiopathic or mild hyperoxaluria as oxalate excretion >0.50 mmol/1.73 $m^2$/24 h with normal glycolate/L-glyceric acid excretion, hypocitraturia as urinary citrate excretion <1.6 mmol/1.73 $m^2$/24 h, hyperuricosuria as urinary uric acid excretion >486 mmol/1.73 $m^2$/24 h, and cystinuria>316 μmol/24 h.

We also routinely checked urine for xanthinuria and dihydroxyadeninuria alongside with qualitative and, if necessary, quantitative individual urine amino acid excretion. Urine saturation for calcium oxalate, calcium phosphate, and urate was calculated by EQUIL2 computer program (normal values depending on age and ion pairs, for calcium oxalate generally <10) three times [13, 47]. Urine output basic formula of 0.5 $cm^3$/kg/h was used for estimation of standard diuresis (>25 ml/kg/24 h); decreased urine volume considered <20 ml/kg/24 h (adequate sampling checked by urine creatinine excretion). Stone samples obtained from 28 children by means of spontaneous passage, extracorporeal shock wave lithotripsy (ESWL), open surgery, and endoscopic evacuation were analyzed by infrared spectroscopy. Increased fluid intake (≥2.0 l/$m^2$/24 h with urine flow output >1 ml/kg/h), individual nutritionally balanced mixed diet with reduced sodium (<3 mEq/kg/24 h with maximum of 2.5 g/24 h) and moderate animal protein intake not affecting their normal development and growth, moderate sucrose and ascorbate intake, together with stimulation of plain water intake instead of sweetened beverages were recommended for all children [3, 10, 23, 35, 39, 43, 45]. In children with increased risk of urinary stone recurrence, namely patients with hyperoxaluria, distal renal tubular acidosis, hypocitraturia and hypercalciuria with bilateral or multiple renal stones, and/or children with constantly elevated urine saturation despite fluid/diet recommendation, additional therapy consisting of individual application of potassium citrate solution (starting dosage, 2 ml/kg) and/or of chlorothiazide until urine saturation and/or selected urine promoter/inhibitor lithogenic stone risk parameter(s) were considered satisfactory for age. Potassium citrate treatment was reduced if children complained of gastric annoyance. In hyperuricosuria, we administered additionally potassium citrate and alkalinization of urine until urine pH value ≥7 was achieved.

First periodic determination of urine saturation, as well as risk of stone formation, were assessed approximately 8 weeks after therapy introduction. During follow-up, the children were continuously monitored for microhematuria on every control alongside with periodic kidney ultrasound examination, and were checked for metabolic disturbances, urine saturation, and stone risk estimation in general [6, 29, 30]. Treatment efficacy was estimated by urinary stone recurrence.

## Results

Urolithiasis was responsible for 2.5/1,000 pediatric hospitalizations, while new cases of urolithiasis was found in 1.1/1,000 admissions in 2011. Comparing these data with data from 2002, two-fold rise of incidence rate from 0.6 (2002) to 1.1 (2011) was observed, especially in girls. Compiling the data from other pediatric institutions in our country, we estimated present overall incidence rate in Croatia as 6.5/100,000 children under 18 years (Table 1).

The patient group consisted of 41 boys and 35 girls (ratio 1.17:1). The male proportion increased (1.45:1) when only patients with positive family history of urolithiasis were considered. The mean age at diagnosis was 9.7 (range 0.8–16) years and follow-up duration 5.3 (range 1.8–10) years.

Most children have unilateral urinary tract stones. Calcium oxalate dihydrate and monohydrate was predominant urinary stone composition (Table 1).

Renal colic was the most common clinical presentation, followed by hematuria, and urinary tract infection, while urinary stones were incidental findings in 8 patients. Hematuria and urinary tract infections were evenly distributed among the age groups. In comparison to other groups, no one child younger than 1 year was without clinical symptoms. These children had the lowest incidence of abdominal pain/restlessness (Table 2). Both ultrasound and contrast diagnostic imaging were used only in children younger than 5 years, with increasing percentage of sole ultrasound in older age groups. Negative imaging due to prior spontaneous stone evacuation was particularly characteristic for children older than 5 years.

Calculi were located in kidney in 52.6 %, in the ureter in 26.3 %, and in bladder in 6.6 % children. Nephrocalcinosis was found in 5.3 % patients. The origin remained unknown in 7 children due to previous spontaneous stone evacuation. Nephrocalcinosis and stone formation in both pyelons characterized children of early childhood, while older children were more prone to ureteral stones. Bladder stones were found exclusively in children older than 10 years.

**Table 1** Demographic and clinical characteristics

| Number of patients | 76 |
|---|---|
| Boys/girls | 41/35, ratio 1.17:1 |
| Mean age at diagnosis (years) | 9.7 (0.8–16) |
| Mean follow-up (years) | 5.3 (1.8–10) |
| Positive family history | 27 (35.5 %) |
| Boys/girls | 16/11, ratio 1.46:1 |
| All cases/hospital admissions | 2.5/1,000 |
| New cases/hospital admissions | 1.1/1,000 |
| Incidence rate 2002:2011 | 0.6:1.1 |
| Compiled incidence rate for Croatia | 6.5/100,000 |
| Age groups (years); *N* (%) | |
| <1 | 6 (7.9) |
| 1–5 | 11 (14.5) |
| 5–10 | 24 (31.6) |
| >10 | 35 (46.0) |
| Number of stones involved; *N* (%) | |
| Unilateral | 50 (65.8) |
| Bilateral | 10 (13.2) |
| Multiple | 9 (11.8) |
| Unclear | 7 (9.2) |
| Urinary stone available for analysis (*N*=28); *N* (%) | |
| Calcium oxalate dihydrate and monohydrate | 21 (75.0) |
| Calcium hydroxycarbonate phosphate | 3 (10.7) |
| Ammonium magnesium phosphate hexahydrate | 1 (3.6) |
| Calcium hydroxy carbonate | 1 (3.6) |
| Uric acid | 1 (3.6) |
| Ceftriaxone | 1 (3.6) |

Spontaneous stone evacuation and/or evacuation of stone after hyperhidration in cases with stones ≤6 mm, occurred in 39 (51.2 %) children. Older children were more prone to spontaneous evacuation of urinary stones. Because of urinary obstruction, ESWL removal of urinary stones was performed in 16 (21.0 %), and surgical and endoscopic stone evacuation in 5 (6.6 %) and 4 (5.3 %) children respectively, all in children older than 1 year. Spontaneous stone resolution was noticed in one child with ceftriaxone urolithiasis (Table 2).

Most common metabolic disturbance was hypercalciuria, present in 36 (47.4 %) children, followed by idiopathic or mild hyperoxaluria, present in 14 (18.4 %) children. There were no patients with cystinuria, xanthinuria or dihydroxyadeninuria. Primary hyperoxaluria and distal renal tubular acidosis were found exclusively in children younger than 1 year, while hypercalciuria and idiopathic or mild hyperoxaluria were found mostly in older children (Table 3). Urine saturation was elevated in 47 (61.8 %) patients. In 5 children it was sole pathological finding. Decreased urine volume was found in 12 (15.8 %) cases.

Fifteen of 76 patients (19.7 %) had anatomic alterations/syndromes besides urinary stones; 5 ureter duplex/fissus, 4 hydronephrosis, 3 vesicoureteral reflux, 1 medullar sponge kidney, 1 caudal regression syndrome and 1 oculocerebrorenal syndrome. Urinary tract anomalies and syndromes were predominantly present in children younger than 5 years. The therapy was sufficient for stone recurrence prevention in 70 (92.1 %) of children. Stones recurred in all children with primary hyperoxaluria, hypocitraturia, and distal renal tubular acidosis, and one child younger than 1 year with hypercalciuria and elevated urine saturation.

## Discussion

Although knowledge on urolithiasis in children has increased in recent years, there is still paucity of epidemiology data of childhood urolithiasis compared to adults. Our data regarding average hospital admissions and incidence rate are comparable to similar studies. Also, like the others, we found rise of incidence rate of childhood urolithiasis in the past decade, especially in girls [26, 38, 45].

The mean age of children in our study was similar as previously reported, with the lowest number of cases among children less than 1 year old [7, 35]. Many studies have reported a male predominance in pediatric urolithiasis, with male/female ratio varying from 1.2:1 to 4:1 [7, 32, 36]. Contrary to older studies, number of boys and girls was almost equal in our study (1.17:1).

However, the male/female ratio fell within range of more usual values (1.45:1) when only patients with positive family history of urolithiasis were considered. Positive family history of urolithiasis had 35.5 % of our patients, pointing to possible genetic tendency toward urolithiasis, especially in males.

In a high socioeconomic conditions stones are mostly located in the upper urinary tract and calcium oxalate predominate, while the characteristics of urolithiasis in low economic conditions are bladder location and frequent ammonium hydrogen phosphate and urate stones [7, 17]. In our study, stones were mostly located in the kidney and ureter (78.9 %), only 6.6 % were found in bladder.

Nephrocalcinosis and stone formation in both pyelons were characteristic for young children, which was similar to other studies [7, 10, 20, 21, 35]. Predominant constituent was calcium oxalate, found in 75.0 % cases, the percentage significantly higher than 48.7 % found in previous study from Croatia a decade ago [7]. These findings, as well as the low percentage of urinary stones associated with recidivant urinary tract infections among our children are clear indication of continuously improving socioeconomic conditions and success in prevention of recurrent urinary tract infection with resolution of their associated anomalies.

We did not found patients with cystinuria despite thorough metabolic search. However, cystinuria was found in 8 patients

**Table 2** Clinical presentation, diagnostics, location, and evacuation of urinary stones according to children's age: <1, 1–5, 5–10, and >10 years

| | <1 year | | 1–5 year | | 5–10 year | | >10 year | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Clinical presentation | | | | | | | | | | |
| Abdominal pain/restlessness | 3 | 50.0 | 7 | 63.6 | 18 | 75.0 | 31 | 88.6 | 57 | 75.0 |
| Hematuria | 3 | 50.0 | 5 | 45.4 | 14 | 58.3 | 23 | 65.7 | 44 | 57.9 |
| Urinary tract infection | 1 | 16.7 | 2 | 18.2 | 3 | 12.5 | 4 | 11.4 | 10 | 13.2 |
| No symptoms | | | 2 | 18.2 | 2 | 8.3 | 4 | 11.4 | 8 | 10.5 |
| Diagnostics | | | | | | | | | | |
| Only ultrasound | | | | | 10 | 41.7 | 17 | 48.6 | 27 | 35.5 |
| Rtg and ultrasound | 6 | 100.0 | 11 | 100.0 | 12 | 50.0 | 13 | 37.1 | 42 | 55.3 |
| Negative imaging (due to prior spontaneous stone evacuation) | | | | | 2 | 8.3 | 5 | 14.3 | 7 | 9.2 |
| Location of urinary stones | | | | | | | | | | |
| Pyelon | | | 5 | 45.4 | 13 | 54.2 | 15 | 42.8 | 33 | 43.4 |
| Both pyelons | 3 | 50.0 | 2 | 18.2 | 1 | 4.2 | 1 | 2.9 | 7 | 9.2 |
| Ureter | | | 3 | 27.3 | 8 | 33.3 | 9 | 25.7 | 20 | 26.3 |
| Bladder | | | | | | | 5 | 14.3 | 5 | 6.6 |
| Nephrocalcinosis | 3 | 50.0 | 1 | 9.1 | | | | | 4 | 5.3 |
| Unknown (due to prior spontaneous evacuation) | | | | | 2 | 8.3 | 5 | 14.3 | 7 | 9.2 |
| Evacuation of urinary stones | | | | | | | | | | |
| Hydration and spontaneous evacuation | | | 2 | 18.2 | 14 | 58.3 | 23 | 65.7 | 39 | 51.3 |
| ESWL | | | 5 | 45.4 | 3 | 12.5 | 8 | 22.9 | 16 | 21.0 |
| Surgical evacuation | | | 2 | 18.2 | 3 | 12.5 | | | 5 | 6.6 |
| Endoscopic evacuation | | | | | 1 | 4.2 | 3 | 8.6 | 4 | 5.3 |
| Spontaneous resolution | | | | | | | 1 | 2.9 | 1 | 1.3 |
| Negative evacuation including nephrocalcinosis | 6 | 100.0 | 2 | 18.2 | 3 | 12.5 | | | 11 | 14.5 |

inside close family related and isolated island communities in previous study from Croatia [7].

Renal colic is the leading clinical sign of pediatric urolithiasis [7, 10, 45]. However, as a first sign abdominal pain is rarely noticed in early infancy and is probably underdiagnosed by pediatricians. We interpreted restlessness as an equivalent of abdominal pain in children younger than 1 year.

Urinary tract infections were equally distributed among all age groups and in accordance to other studies less than expected, probably also reflecting improving socioeconomic conditions with transitions of etiology of stone formation over time from infectious to metabolic causes [7, 9, 37].

During recent years, sole ultrasound imaging for detection of urinary stones is gaining importance [11, 21, 33]. We found that for younger children and ureteral stones ultrasound imaging as difficult for stone detection. Other imaging modalities are necessary in such cases. Due to limited diagnostic resources in collaborating institutions where patients were initially admitted, i.v. urography was used, although nowadays it is suggested to perform a low enhanced CT even in smaller children. Negative imaging due to spontaneous stone evacuation was noticed only in children older than 5 years.

Higher rate of spontaneous stone evacuation in comparison to previous study from Croatia (51.3:31.8 %) was observed [7]. Children older than 5 years were more prone to spontaneous evacuation of urinary stones, similar to other studies [7, 22, 34, 35]. Contrary to other studies, spontaneous passage of urinary stones were not observed in children under 1 year of age [5, 20]. As a relatively recently introduced method of stone removal in children in Croatia, ESWL proved as suitable for children older than 1 year. A particular improvement is the use of recently introduced endoscopic stone removal (now available only for children <10 years) [18].

We found metabolic abnormalities in 73.7 % of the studied children. Idiopathic hypercalciuria was the most frequent metabolic risk factor found, similarly as in other studies [2, 7, 15, 40]. The second main metabolic disorder identified in the study group was idiopathic or mild hyperoxaluria. Urinary oxalate excretion was found increased in approximately 11 to 32 % children with urolithiasis [19, 31, 46]. In our previous study of

**Table 3** Metabolic disturbances, other stone risk predisposition, kidney and urinary tract abnormalities, stone recurrence, and treatment according to children's age: <1, 1–5, 5–10, and >10 years

| | <1 year | | 1–5 year | | 5–10 year | | >10 year | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Metabolic disturbances | | | | | | | | | | |
| Hypercalciuria | 1[a] | 16.7 | 5 | 45.4 | 12 | 50.0 | 18 | 51.4 | 36 | 47.4 |
| Idiopathic or mild hyperoxaluria | | | 2 | 18.2 | 5 | 20.8 | 7 | 20.0 | 14 | 18.4 |
| Primary Hyperoxaluria | 2[a] | 33.3 | | | | | | | 2 | 2.6 |
| Hypocitraturia | | | 1[a] | 9.1 | 1[a] | 4.2 | | | 2 | 2.6 |
| Hyperuricosuria | | | | | | | 1 | 2.9 | 1 | 1.3 |
| Distal renal tubular acidosis | 1[a] | 16.7 | | | | | | | 1 | 1.3 |
| Other stone risk predisposition | | | | | | | | | | |
| Urine saturation elevated | 3 | 50.0 | 7 | 63.6 | 16 | 66.7 | 21 | 60.0 | 47 | 61.8 |
| Urine volume less than average | | | 2 | 18.2 | 4 | 16.7 | 6 | 17.1 | 12 | 15.8 |
| Kidney and urinary tract abnormalities | | | | | | | | | | |
| Medullar sponge kidney | 1 | 16.7 | | | | | | | 1 | 1.3 |
| Vesicoureteral reflux | | | 1 | 9.1 | 1 | 4.2 | 1 | 2.9 | 3 | 3.9 |
| Ureter duplex/fissus | | | 1 | 9.1 | 2 | 8.3 | 2 | 5.7 | 5 | 6.6 |
| Hydronephrosis | | | 2 | 18.2 | 1 | 4.2 | 1 | 2.9 | 4 | 5.3 |
| Caudal regression syndrome | | | | | | | 1 | 2.9 | 1 | 1.3 |
| Oculocerebrorenal syndrome | 1 | 16.7 | | | | | | | 1 | 1.3 |
| Treatment | | | | | | | | | | |
| Increased fluid intake, diet, urine saturation control alone | 2 | 33.3 | 7 | 63.7 | 16 | 66.7 | 25 | 71.4 | 50 | 65.8 |
| Citrate administration | 4 | 66.7 | 4 | 36.4 | 6 | 25.0 | 6 | 17.1 | 20 | 26.3 |
| Thiazide administration | 3 | 50.0 | 4 | 36.4 | 2 | 8.3 | 3 | 8.6 | 12 | 15.1 |
| Aldactone | | | | | | | 1 | 2.9 | 1 | 1.3 |

[a] Recurrent urinary stones after therapy administration

interaction of calcium, oxalate, and citrate in idiopathic calcium urolithiasis in children, we showed that in patients with low urinary calcium, a major role in lithogenesis belongs to oxalate, alone in some patients and in conjunction with citrate in others [30].

Several recent studies found hypocitraturia as the most commonly identified metabolic abnormality in children with urolithiasis [13, 14, 16, 19, 24, 44–46]. We could not confirm this finding. Hypocitraturia was found in only 2.6 % of the studied patients. Obviously, the frequency of a particular metabolic abnormality is different in various populations, depending on differences in genetics, environment, and diet. The low stone recurrence rate in our children seems to support lack of hypocitraturia among our patients [13, 42].

An imbalance between urinary promoting and inhibiting factors might be more important in urinary stone formation than a disturbance of any single substance. In our previous studies, we showed that the best estimation of the relative risk of urolithiasis can be made after urine saturation for calcium oxalate calculated with the computer program EQUIL2 [29, 47]. In present study, 61.8 % of patients had elevated urine saturation for calcium oxalate [12, 25].

Urinary tract anomalies/syndromes which would lead to urinary stasis and calculus formation were present in 19.7 % of the cases in the present study, which is similar to other studies [7, 41]. Pyeloureteral duplication was the most frequent one, followed by vesicoureteral reflux.

Data on conservative treatment in children with urolithiasis are limited. We treated all our patients conservatively with increased fluid intake and/or dietary recommendation and potassium citrate solution and/or chlorothiazide administered additionally only in toddlers, children with primary hyperoxaluria, renal tubular acidosis, hypocitraturia and hypercalciuria with bilateral or multiple renal stones, and/or children with constantly elevated urine saturation despite fluid/diet recommendation [1, 8, 25]. Such therapy successfully prevented urinary stone recurrence for the most of our patients with low overall recurrence. Strong tendency to stones recurrence was noticed only in genetic metabolic disorders, such as primary hyperoxaluria and distal renal tubular acidosis.

Also, stones recurred in all children with hypocitraturia despite adequate citrate administration, the finding also noticed by other authors [4, 14, 41]. It might be that in these cases, an incomplete dRTA with hypocitraturia in the absence of an overt systemic acidosis and hypokalemia was overlooked, as it has been recently well pointed [11].

We consider the average follow-up of 5 years and 3 months with 20.8 % of our patients with even longer period of follow-

up (8–10 years) promising for conclusion of nonrecurrence. However, since stones can recur after prolonged period of time, further follow-up is needed especially during early adult age [11, 27]. We are fully aware of difficulties in lifelong compliance with fluid/diet recommendations [1]. It requires patience and careful advices from skilled nutritionist which role as a part of medical team in treatment of children with urolithiasis is invaluable. For treatment and prevention of stone recurrence, in addition to selected urine promoter/inhibitor of lithogenic stone risk parameters, urine saturation determination should be included in metabolic investigation whenever possible, as it takes into account urine volume.

**Conflict of interest** We, the authors, declare that we do not received financial support from any organization for this article.

## References

1. Alon US (2009) Medical treatment of pediatric urolithiasis. Pediatr Nephrol 24(11):2129–2135
2. Alpay H, Ozen A, Gokce I, Biyikli N (2009) Clinical and metabolic features of urolithiasis and microlithiasis in children. Pediatr Nephrol 24:2203–2209
3. Assimos DG, Holmes RP (2000) Role of diet in the therapy of urolythiasis. Urol Clin North Am 27(2):255–268
4. Bak M, Ural R, Agin H, Serdaroglu E, Calkavur S (2009) The metabolic etiology of urolithisis in Turkish children. Int Urol Nephrol 41:453–460
5. Bastuğ F, Gündüz Z, Tülipar S, Poyrazoglu H, Düsünsel R (2012) Urolithiasis in infants: evaluation of risk factors. World J Urol. doi: 10.1007/s00345-012-0828-y
6. Batinić D, Milošević D, Blau N, Konjevoda P, Štambuk N, Barbarić V et al (2000) Value of the stone promoters/inhibitors ratios in the estimation of the risk of urolithiasis. J Chem Comput Sci 40(3): 607–610
7. Biocić M, Saraga M, Kuzmić AC, Bahtijarević Z, Budimir D, Todorić J et al (2003) Pediatric urolythiasis in Croatia. Coll Antropol 27(2):745–752
8. Borghi L, Meschi T, Amato F, Briganti A, Navarini A, Giannini A (1996) Urine volume, water and recurrences in idiopathic calcium nephrolithiasis. A 5-year randomized prospective study. J Urol 155: 839–843
9. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, Long L et al (2010) Hospitalizations for pediatric stone disease in United States, 2002–2007. J Urol 183:1151–1156
10. Clayton DB, Pope JC (2011) The increasing pediatric stone disease problem. Ther Adv Urol 3(1):3–12
11. Copelovitch L (2012) Urolithiasis in children. Pediatr Clin North Am 59(4):881–896
12. Defoor W, Asplin J, Jackson E, Jackson C, Reddy P, Sheldon C, Erhard M, Minevich E (2006) Urinary metabolic evaluations in normal and stone forming children. J Urol 176:1793–1796
13. DeFoor WR, Jackson E, Minevich E, Caillat A, Reddy P, Sheldon C, Asplin J (2010) The risk of recurrent urolithiasis in children is dependent on urinary calcium and citrate. Urology 76:242–245
14. Domrongkitchaiporn S, Stitchantracul W, Kochakarn W (2006) Causes of hypocitraturia in recurrent calcium stone formers: focusing on urinary potassium excretion. Am J Kidney Dis 48(4):546–554
15. Dursun I, Poyrazoglu HM, Dusunsel R, Gunduz Z, Gurgoze MK, Demirci D et al (2008) Pediatric urolithiasis: an 8-year experience of single centre. Int Urol Nephrol 40(1):3–9
16. Erbagci A, Erbagci AB, Yilmaz M, Yagci F, Trakcioglu M, Yurtseven C et al (2003) Pediatric urolithiasis—evaluation of risk factors in 95 children. Scand J Urol Nephrol 37:129–133
17. Faerber GJ (2001) Pediatric urolithiasis. Urology 11:385–389
18. Granberg CF, Baker LA (2012) Urolithiasis in children: surgical approach. Pediatr Clin North Am 59(4):897–908
19. Gürgöze MK, Sari MY (2011) Results of medical treatiment and metabolic risk factors in children with urolithiasis. Pediatr Nephrol 26:933–937
20. Gür-Güven A, Koyun M, Baysal YE, Akman S, Alimoglu E, Akbas H et al (2010) Urolithiasis in the first year of life. Pediatr Nephrol 25: 129–134
21. Hoppe B, Kemper MJ (2010) Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 25: 403–413
22. Kalorin CM, Zabinski A, Okpareke I, White M, Kogan BA (2009) Pediatric urinary stone disease. Does age matter? J Urol 181: 2267–2271
23. Kant AK, Graubard BI (2010) Contributors of water intake in US children and adolescents: associations with dietary and and meal characteristics—National Health and Nutrition Examination Survey 2005–2006. Am J Clin Nutr 92:887–896
24. Kovacevic L, Wolfe-Christiansen C, Edwards L, Sadraps M, Lakshmanan Y (2012) From hypercalciuria to hypocitraturia—a shifting trend in pediatric urolithiasis? J Urol 188(4 suppl): 1623–1627
25. Lande MB, Varade W, Erkan E, Niederbracht Y, Schwartz GJ (2005) Role of urinary supersaturation in the evaluationof children with urolithiasis. Pediatr Nephrol 20:491–494
26. Lopez M, Hoppe B (2010) History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol 25(1):49–59
27. Lotan Y (2009) Economics and cost of care of stone disease. Adv Chronic Kidney Dis 16:5–10
28. Matlaga BR, Schaeffer AJ, Novak TE, Trock BJ (2010) Epidemiologic insights into pediatric kidney stone disease. Urol Res 38(6): 453–457
29. Milošević D, Batinić D, Blau N, Konjevoda P, Štambuk N, Votava-Raić A et al (1998) Determination of urine saturation with computer program Equil 2 as a method for estimation of the risk of urolithiasis. J Chem Inf Comput Sci 38(4):646–650
30. Milošević D, Batinić D, Konjevoda P, Blau N, Štambuk N, Lj N et al (2003) Analysis of calcium, oxalate, and citrate interaction in idiopathic calcium urolithiasis in children. J Chem Inf Comput Sci 43(6): 1844–1847
31. Neuhaus TJ, Belzer T, Blqau N, Hoppe B, Sidhu H, Leumann E (2000) Urinary oxalate excretion in urolithiasis and nephrocalcinosis. Arch Dis Child 82:322–326
32. Novak TE, Lakshmanan Y, Trock BJ, Gearhart JP, Matlaga BR (2009) Sex prevalence of pediatric stone disease in the United States: an epidemiologic investigation. Urology 74(1):104–107
33. Passerotti C, Chow JS, Silva A, Schoettler CL, Rosoklija I, Perez-Rosello J et al (2009) Ultrasound versus computerized tomography for evaluating urolithiasis. J Urol 182(4 Suppl):1829–1834
34. Pietrow PK, Pope JC 4th, Adams MC, Shyr Y, Brock JW 3rd (2002) Clinical outcome of pediatric stone disease. J Urol 167:670–673
35. Sas DJ (2011) An update on the changing epidemiology and metabolic risk factors in pediatric kidney stone disease. Clin J Am Soc Nephrol 6(8):2062–2068
36. Scales CD Jr, Curtis LH, Norris RD, Springhart WP, Sur RL, Schulman KA et al (2007) Changing gender prevalence of stone disease. J Urol 177(3):979–982

37. Schissel BL, Johnson BK (2011) Renal stones: evolving epidemiology and management. Pediatr Emerg Care 27(7):676–681
38. Sharma AP, Filler G (2010) Epidemiology of pediatric urolithiasis. Indian J Urol 26(4):516–522
39. Siener R, Hesse A (1993) Einfluβ verschiedener kostformen auf die harnzusammen-setzung und das kalziumoxalat-steinbildungsrisiko. Z Ermährungswiss 32:46–65
40. Spivacow FR, Negri AL, del Valle EE, Calvino I, Fradinger E, Zanchetta JR (2008) Metabolic risk factors in children with kidney stone disease. Pediatr Nephrol 23:1129–1133
41. Sternberg K, Greenfield SP, Williot P, Wan J (2005) Pediatric stone disease: an evolving experience. J Urol 174:1711–1714
42. Strohmaier WL, Seilnacht J, Schubert G (2012) Urinary stone formers with hypocitraturia and "normal" urinary pH are at high risk for recurrence. Urol Int 88(3):294–297
43. Taylor EN, Stampfer MJ, Curhan CC (2004) Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. J AM Soc Nephrol 15:3225–3232
44. Tefekli A, Esen T, Ziylan O, Erol B, Armagan A, Ander H, Akinet N (2000) Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: is there any difference. Urol Int 459:1–10
45. Trinchieri A (2008) Epidemiology of urolythiasis: an update. Clin Cases Miner Bone Metab 5(2):101–106
46. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, Trachtman H (2007) Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol 177: 2300–2305
47. Werness P, Brown CM, Smith LH, Finlayson B (1985) EQUIL II: a BASIC computer program for the calculation of urinary saturation. J Urol 134:1242–124