Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). Compared to adults, UL in childhood is less common, and it is believed to be around 5% in industrialized countries, while the incidence of NC is even lower except for critically ill premature infants, in whom it may reach 64%. The formation of UL and NC is caused by increased concentrations of relevant solutes, and their aggregations and adherence to renal tubule cells is facilitated by factors such as urine pH, inability of natural crystallization inhibitors, stasis of urine, as well as renal tubule damage. UL is associated with significant morbidity because of pain, susceptibility to urinary tract obstruction and infections, and the necessity of surgical procedures. NC is usually asymptomatic but is frequently progressive, and leads to chronic renal failure more often than UL. Although other imaging modalities can be used in the diagnosis of renal stone disease, ultrasound has the least risk and is most cost-effective. The majority of cases of UL and NC in children is of metabolic origin; thus, they are prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation. Genetic source of renal stone disease is suspected in the following conditions: early onset, familial prevalence, familial consanguinity, multiple or recurrent stones, and NC. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.

Keywords: nephrolithiasis; nephrocalcinosis; metabolic disorders; children; chronic renal failure

INTRODUCTION

Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). UL is characterized by stones that may be found anywhere in the urinary tract, including kidney and/or ureter or bladder, while NC is defined as calcium salt deposition in the renal parenchyma including the tubular epithelium and interstitial renal tissue [1]. Both UL and NC may be discovered in children of all ages. Although other imaging modalities can be used in the diagnosis of UL/NC, ultrasound has the least risk and is the most cost-effective.

UL/NC is associated with significant morbidity because of pain, susceptibility to urinary tract infections, the necessity of surgical procedures, and/or progression to chronic kidney failure. The most cases of UL and NC in children are of metabolic origin and are thus prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation.

There are important differences of UL and NC in children compared to those in adults. In this review article, the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of the pediatric renal stone disease are discussed. The most attention is paid to the hypercalcicuric renal stone diseases, as these are more likely to present in childhood.

EPIDEMIOLOGY

Compared to adults, UL in childhood is less common, and it is believed to be approximately 10% of that in adults, which is around 5% in industrialized countries [2–6]. The infants constitute up to one third of all pediatric UL patients [3, 4]. Overall, reported incidence of pediatric UL varies from 5.6 to 36 per 100,000 children and adolescents younger than 18 years [5, 6]. The differences in incidence rates reported in children with UL reflect differences in genetic, geographic, and socioeconomic background, but also depend on the design and the time of the study [7]. Endemic UL is found in Southeast Asia, the Middle East, India, and Pakistan, while it is uncommon in children of African descent. It is very likely that the high consanguinity rate contributes to the higher incidence of UL/NC among ethnic groups that live in the Middle East and Asia. Additionally, the endemic calculi observed in these parts of the world are composed predominantly of ammonium and uric acid, and seem to correlate with dietary habits, malnutrition, urinary tract infections, and hot climate. Epidemiology of UL in the European population of the 19th century is similar to that of the 20th century population in Asia [8]. Changes that have occurred in the socio-economic sphere, as well as their consequences, primarily in dietary habits (food rich in proteins and calories), have influenced the incidence, the site (decreased rate of bladder stones) and chemical composition of calculi (raising rate of calcium oxalate and...
calcium phosphate stones) [7]. As in adults, an increased trend of UL incidence, the so-called "stone wave," has also been observed in children [9–15]. VanDervoort et al. [10] demonstrated that pediatric UL increased almost five-fold over the last decade in the United States. An increasing incidence of UL may be explained at least partially by the increasing rate of routine ultrasound examination in children with nonspecific symptoms, as well as with specific ones. As in adults, UL is more common in males than in females, although there are some opposite findings [12, 16]. Pediatric UL morbidity is responsible for 1/685 pediatric hospitalizations in the United States and for 2.5/1,000 pediatric hospitalizations in Croatia [11, 17].

The incidence of NC in children is even less known than that of UL due to its typically asymptomatic course. Thus, NC diagnosis is usually made accidentally by ultrasound examination for other reasons. Due to the increasing application of ultrasound in recent times, NC is more frequent than previously revealed. NC epidemiology in neonates is much better known than in older children, especially in premature babies. It is all the greater if the gestational age and birth body weight of the newborn is less and its condition is more critical [18]. Jacinto et al. [19] reported NC incidence of 64% in premature infants at a mean age of 39.3 ± 26.7 days of life. Infants with NC had shorter gestations (28.2 ± 1.8 vs. 31 ± 1.4 weeks) and lighter birth weights (924 ± 195 vs. 1,338 ± 100 g) than those infants without renal calcifications [19]. In another study, 26.6% of 79 infants born at less than 32 weeks' gestation developed NC [20]. Affected infants were significantly smaller (mean birth weight 940 g) and significantly less mature (mean gestation 26.9 weeks). Multivariate analysis showed that the strongest clinical indicator of NC was the duration of oxygen treatment. Infants who still required oxygen treatment at 28 days of life had a 62% chance of developing renal calcification [20]. Other predisposing factors for NC in newborns are the use of diuretics (furosemide), corticosteroids, parenteral nutrition, and hypocitraturia.

**PATHOPHYSIOLOGY**

A primary event in the formation of UL and NC is the increased concentration of relevant solutes (calcium phosphate, calcium oxalate, sodium urate, cystine, or other substances) in urine above their saturation threshold due to their increased rate of urinary excretion and/or a low urine volume. The formation of crystals of the relevant salts, their aggregations and adherence to the renal tubule cells are also influenced by other factors such as urine pH, inability of natural crystallization inhibitors (citrate, pyrophosphate, sulfate, and magnesium), stasis of urine, as well as renal tubule damage (due to urinary tract infections or some drugs). Crystal binding to the surface of tubular cells is facilitated by a number of luminal membrane molecules, including acidic fragment of nucleolin-related protein, annexin-II, osteopontin, and hyaluronan, which are exclusively expressed at the luminal surface of regenerating/(re)differentiating renal tubular cells [21].

Calcium oxalate is the predominant constituent of at least 75% renal calcifications in pediatrics as well as in adults from industrialized countries [21]. However, the initial role in their formation belongs to calcium phosphate crystals, which start forming apatite plaque (Randall plaques) at the basement membrane of the thin loops of Henle, location predisposed to urothelial erosion due to the urine flux [22]. Aggregations of calcium oxalate crystals at apatite plaques provide further stone formation attached to the papillary tip of the kidney. It is considered that calcium phosphate stones are developed from crystal aggregates deposited at the tip of the Bellini ducts [21].

The kidney itself has a great role in renal stone diseases in association with calcitropic hormones such as vitamin D, and parathyroid hormone. The intrinsic renal calcium-sensing receptor (CaSR) feedback system, the regulation of paracellular calcium transport involving claudins, and new paracrine regulators such as klotho, give kidney a crucial position not only in modulation of calcium but also of calcium homeostasis [23]. Genetic disorders in any of these systems may cause calcium nephropathy.

**ETIOLOGY**

As compared with the adult population, a higher proportion of pediatric patients have a well-defined etiology of renal stones. The etiology may be classified as metabolic, infection-related, structural urinary anomalies causing obstruction, or idiopathic. Metabolic abnormalities account for 25–96% of UL/NC, while urinary tract infection and anatomical obstructive abnormalities account for 25% and 30%, respectively [24, 25]. Metabolic alterations include hypercalciuria, hypocitraturia, hyperuricosuria, phosphaturia with hypophosphatemia, distal renal tubular acidosis, idiopathic infantile hypercalcinemia, Bartter and Dent diseases, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, cystinuria, hyperoxaluria, and renal hypouricemia [26–31]. Heritability has been one of the strongest risks for UL/NC; 35–65% of affected patients will have relatives with UL/NC, compared with 5–20% of those without renal stone who have relatives with UL/NC [6, 27]. At least 30 genes have been shown to cause monogenic UL/NC by autosomal-dominant, autosomal-recessive, or X-linked transmission [28]. Polygenic disorders have also a significant role in UL, such as idiopathic hypercalciuria, but they are less cleared.

The study by Halbritter et al. [32], which included an international cohort of 272 patients with UL/NC, has shown that the percentage of monogenic cases was 11.4% in adult and 20.8% in pediatric patient cohorts. Recessive monogenic diseases typically manifest earlier in life than dominant monogenic diseases [33]. In more than 40% of the cases in the aforementioned study, the genetic diagnoses contributed a new aspect to the previously established clinical diagnosis, suggesting practical implications, such as avoiding vitamin D (CYP24A1), initiating audiometry (ATP6V1B1), excluding the risk of recurrence in renal transplants (CLCN5 or CLDN16), or pyridoxine sensitivity
in the presence of AGXT allele (Gly170Arg [32]. Based on
the study results, Braun et al. [33] give recommendation for
clinicians to be aware of the genetic source of UL/NC in the
following conditions: early onset, familial prevalence, fa-
milial consanguinity, multiple or recurrent stones, and NC.

Hypercalciuria is the commonest metabolic abnormality
causing UL in children. It may be associated with increased,
decreased, or normal serum calcium levels (Tables 1–3).
Idiopathic hypercalciuria (IH) is defined by hypercalciuria,
normocalcemia, and the absence of diseases known to cause
increased urine calcium excretion. In children, hypercalci-
uria is diagnosed if the urine calcium excretion is ≥ 0.1
mmol (≥ 4 mg)/kg/day in at least two separate collections
of urine during 24 hours (24h). Adequate collection is esti-
mated via measuring 24h-urine creatinine of 0.1–0.2 mmol/
kg/24h. In situations where 24h-urine collection is not
possible, random urine measurements are implemented,
using spot urine ratio of the calcium and creatinine and
comparing it with its age-related reference values (Table 4)
[34]. Pathogenesis of IH is very complex and many poten-
tial factors can be involved, such as polymorphisms of the
gene coding for proteins regulating tubular phosphate and
calcium reabsorption [vitamin D receptor (VDR), SLC34A1,
SLC34A4, CLDN14, and CaSR] and those responsible for
proteins preventing calcium salt precipitation (CaSR,
MGP, OPN, PLAU, and UMOD) or gene coding for a water chan-
nel in the proximal tubele (AQP1) [35]. Furthermore, in
families with an autosomal dominant mode of IH, inheri-
tance connection between IH and loci on chromosome
1q23.3-q24, which contains the human soluble adenyl cyclase
gene, chromosome 12q12-q14, which contains the
VDR gene and chromosome 9q32.2-q34.2, were established
[27]. Environmental factors may also significantly affect
renal stone formation. Nutrient intake may change urine
composition, but may also influence gene expression by
epigenic mechanisms [35].

Table 1. Hereditary diseases associated with hypercalcemia and hypercalciuria (modified [27])

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical feature</th>
<th>Mode of inheritance</th>
<th>Gene product</th>
<th>Chromosomal location of the gene</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIHP</td>
<td>Familial isolated parathyroid tumors</td>
<td>A-r/A-d</td>
<td>menin</td>
<td>11q13</td>
<td>PTH increased</td>
</tr>
<tr>
<td>MEN1</td>
<td>Parathyroid hyperplasia and/or tumors associated with pituitary and pancreaticoduodenal neuro-endocrine tumors</td>
<td>A-d</td>
<td>menin</td>
<td>11q13</td>
<td>PTH increased</td>
</tr>
<tr>
<td>MEN2a</td>
<td>Parathyroid tumors with medullary thyroid cancer and pheochromocytoma</td>
<td>A-d</td>
<td>ret</td>
<td>10q11.2</td>
<td>PTH increased</td>
</tr>
<tr>
<td>HPT-JT</td>
<td>Parathyroid tumors with ossifying fibromas of the jaw</td>
<td>A-d</td>
<td>parafibromin</td>
<td>1q31.2</td>
<td>PTH increased</td>
</tr>
<tr>
<td>IHH</td>
<td>Idiopathic hypercalciuria with hypercalciuria</td>
<td>A-r</td>
<td>CYP24A1</td>
<td>5q35</td>
<td>1,25(OH)2D3 increased</td>
</tr>
<tr>
<td>Hypophosphemetic nephrolithiasis/ osteoporosis</td>
<td>Renal phosphate leak, hypophosphatemia, hypercalciuria urolithiasis, osteoporosis</td>
<td>A-d/A-r</td>
<td>NPT2a/SLC34A1 solute carrier family 34 (sodium phosphate), member 1</td>
<td>5q35</td>
<td>PTH decreased</td>
</tr>
</tbody>
</table>

A-d – autosomal dominant; A-r – autosomal recessive; FIHP – familial isolated hyperparathyroidism; MEN – multiple endocrine neoplasia; HPT-JT – hyperparathyroidism – jaw tumor syndrome; IHH – idiopathic hypercalciuria with hypercalciuria; CaSR – calcium-sensing receptor; NPT2a – sodium–phosphate co-transporter type 2a; PTH – parathyroid hormone

Table 2. Hereditary diseases associated with hypocalcemia and hypercalciuria

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical feature</th>
<th>Mode of inheritance</th>
<th>Gene product</th>
<th>Chromosomal location of the gene</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHH</td>
<td>Hypocalciemia, hyperphosphatemia, hypomagnesemia</td>
<td>A-d</td>
<td>CaSR</td>
<td>3q21.1</td>
<td>PTH low – normal range</td>
</tr>
<tr>
<td>FHHNC</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis</td>
<td>A-r</td>
<td>PCLN1/CLDN16</td>
<td>3q28</td>
<td>PTH raised</td>
</tr>
<tr>
<td>FHHNC</td>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular abnormalities</td>
<td>A-r</td>
<td>CLDN19</td>
<td>1p34.2</td>
<td>PTH raised</td>
</tr>
<tr>
<td>FIH</td>
<td>Hypoparathyroidism, familial isolated</td>
<td>A-d</td>
<td>GCM2</td>
<td>6p24.2</td>
<td>PTH low</td>
</tr>
<tr>
<td>APECED</td>
<td>Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy</td>
<td>A-r</td>
<td>AIRE</td>
<td></td>
<td>PTH low</td>
</tr>
<tr>
<td>FIH, recessive</td>
<td>Hypoparathyroidism, autosomal recessive</td>
<td>A-r</td>
<td>11p153</td>
<td>PTH</td>
<td>PTH low</td>
</tr>
<tr>
<td>FIH, x-linked</td>
<td>Hypoparathyroidism, familial isolated –x linked</td>
<td>X-r</td>
<td>GCM2</td>
<td>Xq26–q27</td>
<td>PTH low</td>
</tr>
<tr>
<td>FIH, dominant</td>
<td>Hypoparathyroidism, familial dominant</td>
<td>A-d</td>
<td>PTH</td>
<td>11p153</td>
<td>PTH low</td>
</tr>
</tbody>
</table>

A-d – autosomal dominant; A-r – autosomal recessive; X-r – X-linked recessive; ADHH – autosomal dominant hypocalcemia with hypercalciuria; FHHNC – familial hypomagnesemia with hypercalciuria and nephrocalcinosis; FIH – familial isolated hypoparathyroidism; APECED – autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; AIRE – autoimmune regulator; CaSR – calcium-sensing receptor; PCLN1 – paracellin; CLDN16/19 – Claudin 16/19; PTH – parathyroid hormone

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CLINICAL MANIFESTATION

Unlike adults and adolescents, only 10–14% of children with UL have classic renal colic [17, 34, 36]. Exceptionally, UL in children may be manifested by signs and symptoms of post renal acute kidney injury due to urethral or ureteral obstruction of both or single functioning kidney [37]. Instead, microscopic or macroscopic hematuria, flank or abdominal pain, as well as recurrent urinary tract infection, are predominant clinical presentations of UL in children [16]. Hematuria may precede noticeable UL for some time. Recurrent urinary tract infection or unexplained sterile pyuria in young children should arouse suspicion of UL. The recurrence rate of UL may be as high as 50% at five years [27]. In addition, signs and symptoms of lower urinary tract dysfunction, such as nocturnal enuresis and/or diurnal incontinence, suprapubic or urethral pain may be found in about 10% of children with UL [7]. Finally, 10–25% of young children have no symptoms of UL, which then may be discovered as an incidental finding during abdominal ultrasound imaging for any other reason [7, 34, 38].

Nephrocalcinosis is usually asymptomatic or occult symptomatic and is diagnosed incidentally during the search for causes of hematuria, abdominal pains, or sterile leukocyturia. NC is often progressive, and more often than UL leads to chronic renal failure [28, 31, 34, 38].

DIAGNOSTIC EXAMINATION

Given the complexity of children's UL/NC and especially its predominant metabolic hereditary etiology, it is advised, as the best solution, to perform the systemic diagnostic evaluation and personalized treatment in the Center for Pediatric Renal Stone Disease, as it is practiced in some Western countries [36]. System diagnostic evaluation includes a detailed medical history, careful and complete physical examination, followed by imaging studies and specific blood and urine analyses. In medical history, special attention should be given to information on family renal stones, hematuria, renal failure, but also on diet habits, fluid intake, medications, vitamin and mineral supplements,
immobilization, chronic bowel diseases, and, of course, on urological anomalies and urinary tract infections [34].

Diagnostic imaging should start with an ultrasound examination, which is widely available, non-invasive, without ionizing radiation, and very useful for detecting kidney stones, obstructive anomalies, and other aspects of the urinary tract anatomy [34]. Usually, renal ultrasound is the only method required, but for detection of small stones or stones in the ureter, computed tomography (CT) is more sensitive than ultrasound. Conventional radiography, with or without contrast (plain X-ray) may replace CT in infants and young children as it does not require sedation and gives off less ionizing radiation. However, radiolucent uric acid stones cannot be visualized by conventional radiography while struvite (magnesium ammonium phosphate), cystine stones, and stones composed of some drugs (ceftriaxone) can be difficult to detect from the surrounding tissue. For diagnosing NC in children, high-resolution renal ultrasound is the optimal method due to its high sensitivity (96%), and very good specificity (85%) [39].

A complete analysis of the first morning urine is essential in diagnosing UL/NC. By microscopic urine examination it is possible to differentiate glomerular from non-glomerular hematuria, to diagnose crystals (e.g. hexagonal cystine crystals, orange-brown 2,8-dihydroxyadenine), to notice leukocytes and bacteria. Urine pH (done by a glass electrode or by pH paper), urine-specific gravity or osmolality, urine protein and glucose are part of the routine examination of urine. It is important to note that the results of urinalysis are credible only in the absence of urinary tract infection. Therefore, urine culture is checked prior to the chemical urine analysis, which includes measurements of creatinine, calcium, uric acid, oxalic acid, phosphate, magnesium, and citrate. Cystine is examined by nitroprusside test or by amino acid chromatography. Preferably, it should be done for 24 hours, but when this is unavailable, it can be replaced by the spot urine ratio of the test substance and creatinine (Table 4). All patients should also be examined for serum calcium, phosphorus, magnesium, uric acid, alkaline phosphatase, pH, bicarbonate, and creatinine. In patients with hypercalciuria, it is advised to do blood analyses for the parathyroid hormone, vitamin D metabolites, and vitamin A. For the diagnosis of primary hyperoxaluria, it is required to measure plasma

### Table 4. Normal values of solute for 24 hour urine collection, or for spot urine samples: creatinine ratios (solute/creatinine) (modified [34])

<table>
<thead>
<tr>
<th>The age-specific parameter values</th>
<th>Ratio of solute to creatinine mmol/mmol</th>
<th>mg/mg</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>&lt; 0.1 mmol (&lt; 4 mg)/kg/24h</td>
<td></td>
<td>&lt; 12 months &lt; 2 0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After meals with milk, excretion increases up to 40%.</td>
</tr>
<tr>
<td>Oxalates</td>
<td>&lt; 0.5 mmol (&lt; 45 mg)/1.73 m²</td>
<td></td>
<td>0–6 months &lt; 325–360 288–260</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7–24 months &lt; 132–174 110–139</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2–5 years &lt; 98–101 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5–14 years &lt; 70–82 60–65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 16 years &lt; 40 32</td>
</tr>
<tr>
<td>Citrate</td>
<td>&lt; 1.9 mmol (365 mg)/1.73 m² (M); &gt; 1.6 mmol (310 mg)/1.73 m² (F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 180 mg (94 μmol/g (8.84 mmol) creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased: RTA, premature infants, hypokalemia, renal transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphates</td>
<td>&lt; 0.04 mmol (0.8 mg)/kg; &gt; 88 mg (44 mmol)/1.73 m²/24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>There is no data for children &lt; 2 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>&gt; 0.25 0.42</td>
<td></td>
<td>0–5 years</td>
</tr>
<tr>
<td></td>
<td>&gt; 0.15 0.25</td>
<td></td>
<td>&gt; 5 years</td>
</tr>
<tr>
<td>Phosphates</td>
<td>&gt; 0.63 0.25</td>
<td>&gt; 0.13</td>
<td>Magnesium 0.63 0.13</td>
</tr>
<tr>
<td>Sodium</td>
<td>&gt; 0.15 0.25</td>
<td></td>
<td>Magnesium 0.63 0.13</td>
</tr>
<tr>
<td>Potassium</td>
<td>&gt; 0.25 0.42</td>
<td></td>
<td>Magnesium 0.63 0.13</td>
</tr>
<tr>
<td>Acidum uricum</td>
<td>Age &gt; 2 years &lt; 0.56 mg/dl (33 μmol/l) / GFR (ratio × serum creatinine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 815 mg (4.9 mmol/1.73 m²/24h or &lt; 35 mg (0.21 mmol/kg/24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher in children than in adults; there is no data for children &lt; 2 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthine</td>
<td>30–90 μg (20–60 μmol/24h)</td>
<td></td>
<td>Xanthine 30–90 μg (20–60 μmol/24h)</td>
</tr>
<tr>
<td>Cystine</td>
<td>&lt; 60 mg (0.5 mmol)/1.73 m²/24h</td>
<td></td>
<td>10 years &lt; 10 years</td>
</tr>
<tr>
<td></td>
<td>&lt; 10 years &lt; 55 μmol (13 mg)/1.73 m²; &gt; 10 years &lt; 200 (48 mg)/1.73 m²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR – glomerular filtration rate; TmP/GFR – tubular maximum reabsorption rate of phosphate to glomerular filtration rate
and urine oxalate, and glycolate and L-glycerate in urine. Determining intestinal oxalate absorption and stool *Oxalobacter formigenes* colonization is preferable for secondary hyperoxaluria. Finally, genetic tests are required to confirm the clinical diagnosis and are very useful for personalized treatment and preventive strategy [27–33].

**THERAPY**

In cases of acute renal colic, pain is usually very intense due to the irritation of receptors during dilatation of the urinary system and release of pain mediators through to local irritation and swelling of the wall of the renal pelvis or ureter. The use of nonsteroidal antiinflammatory drugs may be indicated as the first choice. Renal stone expulsive treatment may be managed with open surgery, extracorporeal shock wave lithotripsy, laparoscopic or robot-assisted uretero-pyelolithotomy, percutaneous nephrolithotomy, rigid and/or flexible ureteroscopy and medical expulsive treatment (MET) [40]. Choice of treatment for a specific patient is determined based on the renal stone location, its size and composition, urinary system anatomy, as well as available technology, cost of the treatment, experience of the physician, and preferences of both the physician and the patient's parents [40]. Alpha-blockers and calcium channel blockers have been found to be more effective and successful for MET than other drugs (antimuscarinic drugs, phosphodiesterase type-5 inhibitors and steroids) [40]. Both of these eliminate or alleviate uncoordinated contractions induced by the stone and do not affect the normal peristalsis of the ureter. MET may be useful for small stones (5–10 mm) within the distal part of ureter, and are usually applied after the extracorporeal shock wave lithotripsy treatment.

Non-pharmacological measures are still the initial and basic treatment and preventive measures [38]. These include an increase in urine output and crystallization inhibitors, and the setting of optimal urine pH. Increasing the intake of fluids (≈ 3 l/m² of body surface area) provides urine output > 1 ml/kg/h [38]. Reduced intake of table salt (NaCl) and increased potassium intake should maintain the Na/K ratio in urine to < 2.5 [38]. It should not reduce calcium intake below the age-recommended dose (800 mg/day for pre-school and 1,300 mg/day for school age) because of the increased risk for osteopenia and hyperoxaluria. It is also advised to reduce the intake of animal protein. The intake of phytate and magnesium should increase, while the intake of sucrose, fructose, and high doses of vitamin C should be reduced [38].

Pharmacological measures are specific regarding the etiology of UL/NC. For hypercalciuria and/or hypocitraturia, it is advised to give K citrate (0.5–1.5 mEq or 0.1–0.15 g / kg of body weight per day divided into two or three doses each), which is metabolized to bicarbonate in the liver, thus reducing intratubular citrate reabsorption and therefore increasing urinary citrate excretion. Citrate forms a complex with calcium, reducing precipitation of calcium with other substances such as oxalate. Thiazides (hydrochlorothiazide 1–2 mg/kg/day divided into one to two doses) with or without amiloride also decrease calcium urine excretion [38]. In patients with dominant hypercalcinemia, hyperphosphatemia, and hypercalciuria due to a gain-of-function CaSR mutation, vitamin D is not indicated as it worsens hypercalcemia and hypercalciuria. For hypercalciuria + phosphaturia, phosphates are given. Treatment options for the CYP24A1 mutation disorders include avoidance of vitamin D supplementation, sunlight exposure, and tanning beds, along with high water intake, but treatment with the cytochrome inhibitor ketoconazole may be beneficial in severely affected patients [41, 42].

For primary hyperoxaluria type I, in addition to large water intake (> 3 l/m²/day), citrate or orthophosphate, vitamin B₆ (5–20 mg/kg/day) is given, which in about 30% of patients (those with a distinct allele – Gly170Arg) may enhance the reduced activity of alanine/glyoxylate aminotransferase (AGT), thus reducing hyperoxaluria. In others, hepatic AGT activity should be restored by liver transplantation. Sequential liver–kidney or liver combined with kidney transplantation is performed in patients with advanced stages of chronic kidney failure. In secondary (absorptive) hyperoxaluria, it is necessary to treat the primary gastrointestinal disease, to reduce the intake of oxalate in the food, increase the intake of calcium (to bind fatty acids, thereby preventing the intestinal absorption of oxalate), with potassium citrate and probiotics.

Hyperuricosuria is treated with alkalinization of urine (by potassium citrate), dietary purine restriction, and, if needed, allopurinol can be added.

In patients with cystinuria, urine pH should be kept between 7.0 and 7.5 by potassium citrate and bicarbonate, in addition to abundant rehydration. Specific drugs for cystinuria are tiopronin, D-penicillamine and captopril, which cleave cystine into two cysteine-disulfide moieties that are 50-times more soluble than cystine. However, care must be taken of their side effects.

In distal renal acidosis, treatment of acidosis by potassium citrate and bicarbonate is the cornerstone of therapy.

**CONCLUSION**

UL/NC in children is a very important problem due to its complications and possibility to cause chronic renal failure. Every child with renal stone should undergo the diagnostic evaluation. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.
REFERENCES


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САЖЕТАК
Бубрежно камење код деце се испољава као постојање ка-
менићи у бубрезима и уринарним путевима – уролитијаза (УЛ), или као калцификација бубрежног паренхима – нефро-
калциноза (НК). УЛ код деце је ређа у односу на одрасле и из-
носи око 5% у индустријским земљама, а НК је још ређа, осим
код критично болесних прематуруса, код којих може достигти
чак 64%. Формирање УЛ и НК су условљени повећаном кон-
центрацијом соли у урину, а њихова агрегација и адхеренција
за бубрежне тубулске ћелије је олакшана факторима као што
су pH урина, слабост природних инхибитора кристализације,
стаца урина и оштетења тубула. УЛ прати значајан морбиди-
тет због болова, подложности опструкцији и инфекцији ури-
нарног тракта и честих потреба за хируршким интервенција-
ма. НК је обично асимптоматска, али је често прогресивна и
много чешће од УЛ изазива хроничну бубрежну слабост. УЛ и
НК се дијагностикују применом различитих испитивања која
dоју сливу уринарног тракта, а упразнично испитивање је
најмање ризично и најисплатљивије. У већини случајева УЛ и
НК су метаболичког порекла те су склони поновном јављању
и хроничном оштетењу бубрега. Због тога они заслужују,
чак и при првој појави, да се детаљно испита узрок њиховог
настанка. На генетички узрок калкулозе и НК треба помис-
лити у следећим околностима: рана појава, фамилијарно
оптерећење бубрежним болестима, консангвинитет, више
калкулуса или њихово понављање и присуство НК. За све
типове бубрежног камења веома је важна рана дијагноза и
персонална терапија основне болести.
Кључне речи: нефролитијаза; нефрокалциноза; метабо-
личке болести; деца; хронична бубрежна инсуфицијениција

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