Nephrocalcinosis and urolithiasis in children

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The incidence of adult urolithiasis has increased significantly in industrialized countries over the past decades. Sound incidence rates are not available for children, nor are they known for nephrocalcinosis, which can appear as a single entity or together with urolithiasis. In contrast to the adult kidney stone patient, where environmental factors are the main cause, genetic and/or metabolic disorders are the main reason for childhood nephrocalcinosis and urolithiasis. While hypercalciuria is considered to be the most frequent risk factor, several other metabolic disorders such as hypocitraturia or hyperoxaluria, as well as a variety of renal tubular diseases, e.g., Dent's disease or renal tubular acidosis, have to be ruled out by urine and/or blood analysis. Associated symptoms such as growth retardation, intestinal absorption, or bone demineralization should be evaluated for diagnostic and therapeutic purposes. Preterm infants are a special risk population with a high incidence of nephrocalcinosis arising from immature kidney, medication, and hypocitraturia. In children, concise evaluation will reveal an underlying pathomechanism in >75% of patients. Early treatment reducing urinary saturation of the soluble by increasing fluid intake and by providing crystallization inhibitors, as well as disease-specific medication, are mandatory to prevent recurrent kidney stones and/or progressive nephrocalcinosis, and consequently deterioration of renal function.

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In the past decade, a significant increase in both incidence and prevalence of adult urolithiasis (UL) has been noted in industrialized countries. In addition, in pediatric patients, hospitalization for kidney stone disease has steadily increased.[1,2] Definite incidence rates are, however, not available for UL, nor for nephrocalcinosis (NC) in children. The increase of stone disease in adults was most likely related to (changing) environmental factors such as dietary habits, fluid intake, and obesity, all subsumed in the metabolic syndrome. Although this will clearly also gain importance in the pediatric population, genetic and anatomical causes are still the main determinants. UL subsumes stones formed in the kidney but localized anywhere in the urinary tract, as well as primary bladder stones[3] (Figure 1a). Nephrolithiasis describes stones residing in the kidney (Figure 1b–d). NC comprises deposits of calcium salts in the tubules, the tubular epithelium, and/or the interstitial tissue of the kidney[3] (Figure 1e). Although the composition of the deposits mostly remains unclear and cannot be identified by ultrasound, pathologists distinguish between NC due to calcium phosphate and oxalosis due to calcium oxalate deposition. NC can also be classified according to the anatomic area involved. Medullary NC, subdivided into three subtypes according to the degree of echogenicity, is distinguished from cortical (e.g., in acute cortical necrosis) and diffuse NC.[4,5]

EPIDEMIOLOGY

Adult data describe an incidence of UL of approximately 1.5% and a prevalence of 5.2%.[6,7] About 12% of men and 5% of women in industrialized countries will therefore develop a kidney stone at least once in their life.[8] The incidence of UL in pediatric patients is considered to be approximately 10% of that in adults. As incidental discovery occurs in 15–40% of children due to the high proportion of unspecific symptoms, the real incidence in childhood is likely to be underestimated. During past decades, studies reported that 1 in 1000 to 1 in 7500 pediatric hospital admissions were related to UL.[9,10] A recent single-center study reported a nearly fivefold increase in hospital admissions for pediatric UL during the past decade.[1] Another study from the southeast United States, known as the US 'stone-belt', identified an increase of children with UL in an Emergency Room setting from 7.9 to 18.5 per 100,000 from 1996 to 2007. Interestingly, the number of African-American children remained relatively low, 3.2 to 4.5, whereas the number of Caucasian children in

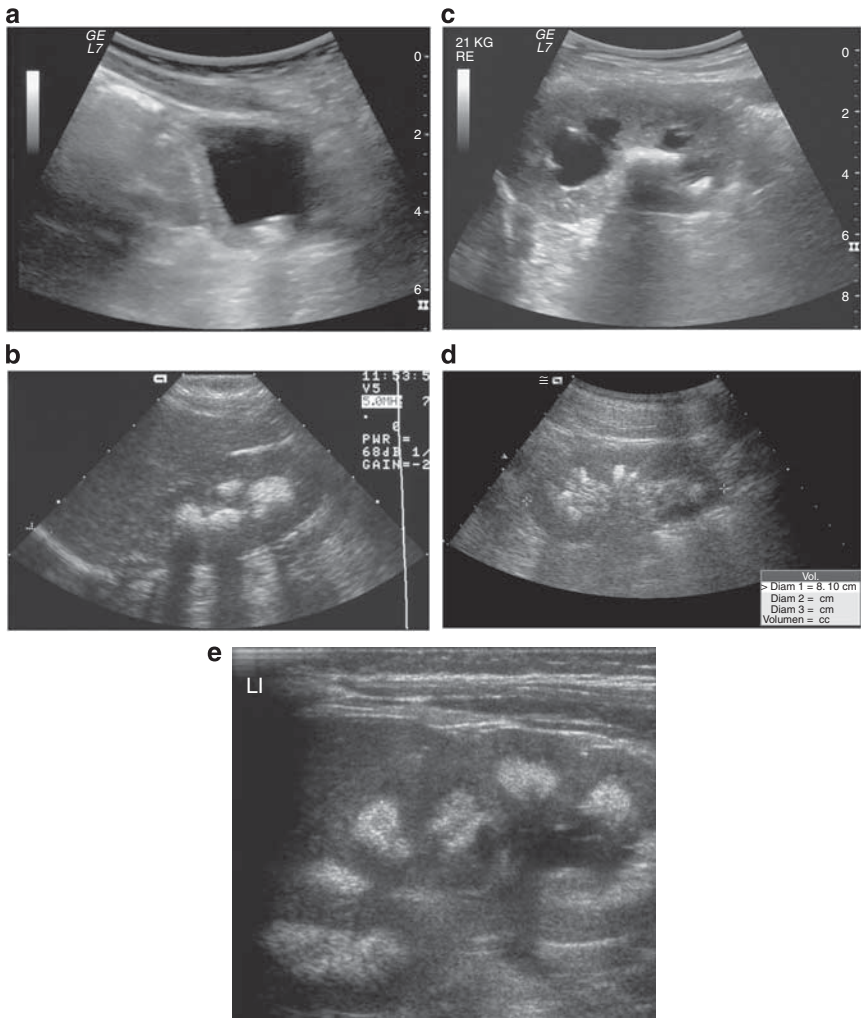

Figure 1 | Urolithiasis and/or nephrocalcinosis in different diseases. (**a**) Bladder stone in a 4-year-old patient with Joubert syndrome after kidney transplantation due to suture *in situ*; (**b**) infectious stones (mixture of struvite and carbonate apatite) in a 9-month-old boy with recurrent urinary tract infections (*Proteus mirabilis*) and proximal ureter stenosis; (**c**) staghorn calculus and nephrocalcinosis in a 7-year-old patient with cystic fibrosis, hyperoxaluria, and hypocitraturia; (**d**) kidney stones and nephrocalcinosis in an 11-year-old patient with primary hyperoxaluria type I; and (**e**) nephrocalcinosis in a 2-year-old patient with familial hypomagnesemia, hypercalciuria, and nephrocalcinosis syndrome.

that setting rose from 10.9 to 26.2 per 100,000 in 2007. Caucasian children are thus 5.6 times more likely to have kidney stones compared with African-American children.[2]

SEX AND AGE

UL and/or NC affect children of all ages.[11] NC seems to primarily appear in the first years of life, which might be due to the fact that it is frequently based on tubulopathies or inborn errors of metabolism (Table 1). Sound data on sex and age distribution are, however, only known for UL. Younger children are described to present with a higher proportion of renal calculi,[12–14] whereas older children rather present with ureteral stones. Contradictory data exist on a higher or equal probability of spontaneous passage in children older or younger than 10 years of age.[13,14] Data on sex distribution have changed over the past years. In adults, a male predominance is no longer found. Interestingly, the risk of stone disease due to increased body mass index and waist circumference is more pronounced in women.[15–18] A recent study analyzed the Kids' Inpatient large-scale pediatric database for sex distribution in more than 2 million children hospitalized because of UL and reported a changing sex distribution according to age.[19] Boys were more frequently affected during the first decade (1.2:1 for 0–5 years, 1.3:1 for 6–10 years), whereas girls were more frequently affected during the second decade of life (0.96:1 for 11–15 years, 0.3:1 for 16–20 years).[19] Data from the southeast United States show even more pronounced changes in sex distribution. Whereas in 1996 the reported incidence in boys (8.0/100,000) did not differ from that in girls (7.7/100,000), the incidence in girls showed a faster and stronger increase to 21.9/100,000 in 2007 (boys 15.3/100,000).[2]

ETIOLOGY

Compared with adults, children are more likely to have an underlying metabolic disorder, and subsequently a higher

Table 1 | Genetic diseases with urolithiasis and/or nephrocalcinosis according to underlying metabolic derangement

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
Hypercalciuria			
Autosomal dominant hypocalcemic hypercalciuria[48]	*CASR*/CaSR, 3q21.1 Gain-of-function mutations usually private mutations leading to leftward shift of extracellular calcium dose–response curve	**ad**	Mild, usually asymptomatic hypocalcemia, hypercalciuria, with elevated serum phosphate and low serum magnesium levels, PTH in the low-normal range *nota bene:* vitamin D substitution will result in excess hypercalciuria, leading to NC, UL and eventually CRF note: inactivating mutations of CaSR increase the threshold for negative feedback and cause hypocalciuric hypercalcemia
Hypercalcemia with hypercalciuria[169]-familial isolated hyperparathyroidism	Menin, 11q13 Parafibromin, 1q31.3 CaSR, 3q21.1	**ad**	Familial isolated parathyroid tumors, inactivating mutations in CaSR
Idiopathic hypercalciuria[170–172]	*SAC*/soluble adenyl cyclase, 1q23.3–q24; sequence variations but no causative mutations	**ad**	Associated with absorptive type of hypercalciuria, normocalcemia, normal PTH levels, low bone mineral density
	VDR/Vitamin D receptor, 12q12–q14, polymorphisms, but no causative mutations	**ad**	Associated with resorptive type of hypercalciuria
	Gene remains to be found, 9q33.2–q34.2 locus	**ad**	Autosomal dominant nephrolithiasis
BS[169]			
Type 1	*SLC12A1*/NKCC2 (bumetanide-sodium-potassium-chloride cotransporter); 15q15–q21.1	**ar**	Classical BS: hypokalemic alkalosis, renal salt wasting, hyperreninemic hyperaldosteronism, hyperprostaglandinemia, hypercalciuria and NC, potential CRF antenatal BS (polyhydramnios, salt wasting, prematurity, volume depletion)
Type 2	*KCNJ*/ROMK (renal outer-medullary potassium channel); 11q24	**ar**	Classical/antenatal BS, hypercalciuria and NC transient neonatal hyperkalemia later evolving into (modest) hypokalemia, potential CRF
Type 3	*CLCNKB*/CLC-Kb (voltage-gated chloride channel); 1q36	**ar**	Mostly classical BS, wide phenotype variation (diagnosis neonatal period to adulthood), less hypercalciuria and NC, potential CRF
Type 4	*BSND*/Barttin; 1q31	**ar**	Usually severe antenatal BS with sensorineuronal deafness, but less hypercalciuria and NC, CRF
Type 5	*CASR*/CaSR, (severe gain-of-function mutations); 3q21.1	**ad**	Early (symptomatic) hypocalcemia and hypercalciuria with NC (see above) followed later by classical BS features
Dent's disease			
Dent 1 (ref. 53)	*CLCN5* chloride/proton antiporter CLC5; Xp11.22 (Dent 1), mutations in 60% of cases	**Xr**	Male gender, FS (aminoaciduria, phosphaturia, glycosuria, kaliuresis, impaired acidification), LMW proteinuria, hypercalciuria (less severe with age), NC/UL, CRF regular
Dent 2 (ref. 173)	*OCRL1* (Dent 2), mutations in 15% of cases	**Xr**	Patients with *OCRL1* mutation and Dent's disease lack cataracts (BS-like phenotype termed BS type 6 was reported in a single Turkish patient with *CLCN5* mutation)
Lowe's (oculorenocerebral) syndrome[174]	*OCRL1*/phosphatidylinositol-4,5-biphosphate-5-phosphatase ocrl1; Xq25	**Xr**	Male gender, congenital cataracts, mental retardation, hypotonia, rickets, proximal tubular defect (bicarbonate, phosphate, aminoaciduria), nephrotic range proteinuria, metabolic acidosis, hypercalciuria and NC/UL, CRF regular
Urolithiasis, osteopetrosis and persistent hypophosphatemia[175]	*NPT2a*/sodium-phosphate-cotransporter type 2a (SLC34A1); 5q35	**ad**	Excess urinary phosphate excretion, hypophosphatemia, elevated 1,25OH vitamin D, elevated AP, suppressed PTH, hypercalcemia and hypercalciuria
Hereditary hypophosphatemic rickets with hypercalciuria[176]	*NPT2c*/sodium-phosphate-cotransporter type 2c (SLC34A3); 9q34	**ar**	Excess loss of urinary phosphate, hypophosphatemia, severe rickets, hypercalciuria but no hypercalcemia, UL
Williams–Beuren syndrome[177]	Continuous gene deletion syndrome (1.55 Mb, including *ELN*, *LIMK1*, *RFC2*); 7q11.23	**Mostly sporadic**	Multisystemic developmental disorder with mental retardation, distinctive neuropsychological profile 'happy party manner', variable cardiovascular findings (aortic stenosis), abnormalities of renal tract and connective tissue, temporary hypercalcemia and hypercalciuria, NC/UL

Table 1 Continued on following page

Table 1 | Continued

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)[178]	*CLDN16*/claudin 16/paracellin 1; 3q27	ar	Symptomatic hypomagnesemia and hypocalcemia, hypercalciuria and NC/UL, distal RTA, regular CRF
FHHNC with ocular involvement[179]	*CLDN19*/claudin 19; 1p34.2	ar	Hallmarks of FHHNC with multiple ocular abnormalities
Wilson's disease[14]	*ATP7B*/copper transporting ATPase 2; 13q14.3	ar	Fanconi syndrome, liver dysfunction, neurological symptoms, Kayser–Fleischer cornea ring, elevated urinary copper excretion-reduced ceruloplasmin, hypercalciuria, UL, NC, CRF
Tyrosinemia type 1 (ref. 14)	*FAH*/fumarylacetone-acetate hydrolase; 15q.23–q25	ar	Fanconi syndrome, rickets, liver failure, coagulopathy, hypercalciuria, UL, NC, CRF
Liddle's syndrome (pseudohyperaldosteronism type 1)[14]	*SCNN1B* and *SCNN1G*/β- and γ-subunits of epithelial sodium channel (ENaC); 16p12	ad	Rare, triad of hypokalemia, alkalosis and sodium-sensitive hypertension, suppressed aldosterone levels, hypercalciuria and NC, risk of CRF, treatment with amiloride (ENaC blocker)
Gordon's syndrome (pseudohypoaldosteronism type 2)[14]	*WNK1* 12p13.3, *WNK4* 17q21.31/serine-threonine kinase	ad	Hyperkalemia, metabolic acidosis (reduced ammonium excretion), hypertension and hypercalciuria (RTA type 4)
Hyperoxaluria			
Primary hyperoxaluria type I (PH I)[76]	*AGXT*/alanin-glyoxylate-aminotransferase; 2q37.3 80–90% of PH cases	ar	Recurrent UL and/or progressive NC, UTI, severe hyperoxaluria (>1 mmol/1.73 m^2 per day), hyperglycolic aciduria, ESRF regular outcome (neonatal period to late adulthood), systemic oxalate deposition with advanced renal failure leads to a multisystemic disease character
Primary hyperoxaluria type II (PH II)[85]	*GRHPR*/glyoxylate reductase/hydroxylpyruvate reductase (GRHPR); 9q11, 10% of PH cases	ar	Hallmarks recurrent UL, NC less frequent, hyperoxaluria plus marked L-glyceric aciduria in most cases, lower ($\sim$20%) risk of ESRF
Primary hyperoxaluria type III (PH III)[85]	*DHDPSL*/4-hydroxy-2-oxoglutarate aldolase; 10q24.2	ar	Likely the second most frequent PH type disease seems to remit with age. No case of ESRF reported (*nota bene*: very limited data)
Atypical PH	Unknown, negative *AGXT*, *GRHPR,* and *DHDPSL* mutational analysis		Hyperoxaluria and clinical features overlapping with PH type I–III Risk of ESRF not defined
Cystinuria			
Cystinuria type I (heterozygotes are silent)[180]	*SLC3A1*/rBAT; 2p16.3, causative mutations result mostly in type I	ar	Impaired renal transport of cystine and dibasic amino acids, high urinary cystine levels
Cystinuria type II (heterozygotes show a variable degree of hypercystinuria)[180]	*SLC7A9*/b0,+ AT; 19q13.1, causative mutations may result in type I phenotype	adip	
Mixed type I/II cystinuria phenotype[180]	All genotypes possible but mostly *SLC7A9* mutations		
Hyperuricosuria			
Lesch–Nyhan syndrome[181]	HPRT/hypoxanthine-guanine-phosphoribosyltransferase; Xq26	Xr	Symptomatic in males, normal at birth followed by progressive psychomotor delay, gout, hyperuricosuria, recurrent UL, automutilation
Partial HPRT deficiency[181]			Hyperuricosuria, wide spectrum of symptoms with asymptomatic course in less severe forms
Glycogenosis type 1a[182]	*G6PC*/glucose-6-phosphatase; 17q21	ar	Episodic severe hypoglycemic, lactic acedemia, hyperuricosuria, hypercalciuria, hypocitraturia, recurrent UL, NC, Fanconi syndrome, FSGS, renal amyloidosis, CRF
Hypouricosuria			
APRT deficiency[183]	*APRT*/adenine-phosphoribosyltransferase; 16q24.3	ar	Urinary accumulation of the insoluble purine 2,8 dihydroxyadenine (round + brown crystals), UL, CRF
Xanthinuria[110]	XDH/xanthine dihydrogenase oxidase; 2p22 (type 1) Type 2 dual deficiency of XDH plus aldehyde oxidase	ar	Noticeable low levels of uric acid in serum and urine, xanthinuria, UL (radiotransparent)
Urate transporter 1 (ref. 184)	SLC22A12/renal urate anion exchanger URAT1; 11q13	ar	Sporadic/familial renal hypouricemia, UL, and risk of exercise-induced ARF

Table 1 Continued on following page

Table 1 | Continued

Entity/disorder	Gene/gene product/locus	Inheritance	Hints and hallmarks
RTA hypocitraturia + hypercalciuria			
RTA[54,185,186]			
RTA type 1	*ATP6V1*/B1 subunit of H+ ATPase; 2cen–q13	ar	Distal RTA, metabolic acidosis (impaired H+ excretion) of early onset with early NC and hearing loss, hypocitraturia, hypercalciuria, UL, NC, hypokalemia, rickets, failure to thrive
	ATPV0A4/ A4 subunit of H+ ATPase; 7q33–34	ar	Later onset of sensorineural deafness (sometimes normal hearing)
	SLC4A1/basolateral Cl/HCO3 exchanger AE1; 17q21–22	ad	Distal RTA of later onset, milder metabolic acidosis, urine pH > 6.1, hypokalemia, hypocitraturia, hypercalciuria, UL, NC, sometimes rickets
	SLC4A1/basolateral Cl/HCO3 exchanger AE1; 17q21–22	ar	Distal RTA of childhood onset, metabolic acidosis plus hemolytic anemia in southeast Asians
RTA type 2	*SLC4A4*/NBC1 sodium bicarbonate cotransporter; 4q21	ar	Proximal RTA, (milder) metabolic acidosis by bicarbonate wasting, hypokalemia, growth retardation, ocular abnormalities, enamel defects, intellectual impairment, less severe hypercalciuria and hypocitraturia
RTA type 3 (mixed type)	*CA2/carboanhydrase 2*	ar	Bicarbonate wasting + inability to acidify the urine: RTA plus osteopetrosis (Guibaud–Vainsel syndrome), intracerebral calcification, growth failure, intellectual impairment, conductive deafness

Abbreviations: AD, autosomal dominant; ADIP, autosomal dominant with incomplete penetrance; AP, alkaline phosphatase; AR, autosomal recessive; ARF, acute renal failure; BS, Bartter syndrome; CaSR, calcium-sensing receptor; CRF, chronic renal failure; ESRF, end-stage renal failure; FS, Fanconi syndrome; FSGS, focal segmental glomerulosclerosis; LMW, low-molecular weight; PTH, parathyroid hormone; RTA, renal tubular acidosis; NC, nephrocalcinosis; UL, urolithiasis; Xr, x-linked recessive. References are imbedded in table.

risk of stone recurrence[16,17] or progression of NC[3,4] (Table 1). Hence, the identification of metabolic abnormalities that predispose to UL/NC is imperative to prevent stone recurrence, which is reported in up to 20–48% of children, or rapid progression of NC.[10,12,20,21] A urinary (metabolic) risk profile was found in up to 76% of children with UL.[14,22] NC does not necessarily lead to renal calculi, and UL may occur in the apparent absence of (macroscopic) NC.[23] Nevertheless, they may appear together in the same patient[11] (Figure 1c, d). The ultrasound picture may suggest NC, but the correct diagnosis would be microcalculi, which may be visualized as tiny hyperechoic spots of <3 mm in diameter on ultrasound, or as small stones of a diameter <2 mm on a low-enhanced computed tomography (CT) or by endoscopic examination.[24–26] Laterality of NC in kidney stone formers was also just recently described.[27] Distinguishing both entities may be problematic even with newer imaging techniques, and hence endoscopic inspection of the papillae may be the only option to truly verify the accurate diagnosis of NC.[27] It was reported that NC may disappear over time;[28,29] however, this was only determined by repeated ultrasound examinations.

Risk factors for UL/NC include genetic abnormalities in epithelial transport, metabolic disturbances, anatomical abnormalities, and urinary tract infections in the majority of pediatric patients. Environmental factors mainly reflected by diet definitively contributed more to the increasing incidence of stone disease in adults, but may gain importance in the pediatric population in the near future, expressed by the increasing numbers of children with obesity or the metabolic syndrome.[30–32]

Great progress has been made in understanding the pathophysiology of stone disease. Randall[33] was the first to describe growing calcium oxalate stones attached to areas of the papillae containing interstitial apatite deposits, which was later confirmed by Evan *et al.*[24] This stone formation/overgrowth on interstitial apatite plaques (Randall's plaques) has recently been described by Coe *et al.*[34] as the first of three possible pathways leading to stone formation. Although this pathway is typical of idiopathic calcium oxalate stone formers, crystal deposition in renal tubules is found in nearly all (other) stone-forming groups. As a third pathway, free solution crystallization is described to be typical of patients with cystinuria or those with secondary hyperoxaluria.[34]

Two crucial processes are believed to form the basis for the development of NC: (1) crystal formation in renal tubules and (2) crystal retention in the distal tubule. In case of an increased bout of lithogenic factors or decreased urine volume, urinary supersaturation leads to crystal formation in the renal tubules. If supersaturation does not exceed a certain (individual) level and duration, non-adherent epithelium, as well as tubular transport mechanisms controlling urine composition and adding crystal inhibitors such as citrate, magnesium and proteins, allow passage of supersaturated urine as well.[35–41] In the absence of a non-adherent, healthy epithelium or in case of failure of these protective tubular mechanisms, crystal retention occurs. This takes place in proliferating or regenerating cells in the distal nephron, which luminally express hyaloronan and osteopontin. The concept of immature/proliferating cells being prone to retain crystals is in accordance with the observation that

preterm and transplant kidneys containing proliferating and/or regenerating cells (due to incomplete nephrogenesis or to ischemia and nephrotoxic immunosuppressants) often experience crystal retention. Next to epithelial disorders, the physiological mechanisms of preventing crystal formation and adhesion can be foiled by high amounts of a soluble due to (1) hyperabsorption (e.g., in vitamin A/D excess, chronic inflammatory bowel disease, small bowel syndrome), (2) overproduction (e.g., primary hyperoxaluria, PH), (3) deranged epithelium (e.g., infection, prematurity), and (4) tubular transport defects (several tubulopathies).

RISK FACTORS (UL and NC)

Hypercalciuria

Hypercalciuria is one of the most frequent risk factors for UL and NC.[42–44] There is no sharp limit between normal (<0.1 mmol/kg body weight per day)[45,46] and abnormal, except for very high excretions (>0.2 mmol/kg per day). *Primary idiopathic hypercalciuria* is the most common cause of calcium-containing stones.[3] It has traditionally been divided into a renal and an absorptive subtype,[47] distinguished by an elevated fasting urinary calcium excretion in the renal subtype. Many pediatric patients, however, cannot easily be classified.

Idiopathic hypercalciuria is considered a multifactorial disease characterized by a complex interaction of environmental and individual factors. Up to 50% of patients have a positive family history.[48,49] Interestingly, calcium excretion correlates positively between parents and their progeny and between siblings, but not between spouses. In addition, it appears that genetically derived risks are greater than diet-related risks.

In the search of genes or polymorphisms explaining the greater susceptibility to renal stone production in patients with common UL, besides other candidate genes, the *calcium-sensing receptor* (*CASR*) gene was also widely analyzed. It is located on chromosome 3q13.3-q2 and encodes for a plasma membrane G-protein-coupled receptor (Table 1). This receptor is activated by binding calcium ions on its extracellular domain. It is widely expressed, regulating, e.g., parathyroid hormone secretion, tubular calcium reabsorption, intestinal calcium absorption, and bone remodeling.[48,49] Activating mutations lead to the autosomal dominant syndrome of familial hypocalcemia with hypercalciuria. Here, hypocalcemia results from inhibiting active and passive calcium reabsorption in the ascending limb of Henle's loop and parathyroid hormone secretion. As bone density was found to be normal or increased,[50] hypercalciuria seems not to originate from bone. Inactivating mutations of *CASR* lead to hypocalciuria and hypercalcemia. Although the *CASR* locus was not associated with idiopathic hypercalciuria or idiopathic calcium UL,[51] interesting data of *CASR* polymorphism were described.[52] A small but significant (12.6%) variance in calciuria was explained by a single-nucleotide polymorphism (SNP) in the *CASR* gene (990Gly SNP), which might lead—when activating—to an increased CASR sensitivity, a decreased calcium reabsorption, and parathyroid hormone secretion.

In the rare but extremely severe X-linked hypercalciuric nephropathy with tubular proteinuria, Dent's disease I, early progressive NC, and renal failure occur.[53] Medullary NC and calcium phosphate stones are common in patients with distal renal tubular acidosis,[54] based on a high urinary pH, hypercalciuria, and hypocitraturia.[55] Medullary NC in combination with cortical NC was described in children with *tyrosinemia*. This rare disease, 1:100,000 live births, is often combined with impaired renal function, aminoaciduria, hypercalciuria, and tubular acidosis. A variety of other genetic disorders leading to hypercalciuria are summarized in Table 1.

There are several clinical entities leading to hypercalcemia with secondary hypercalciuria and the risk of developing NC and/or UL. *Primary hyperparathyroidism*, although the most frequent cause of hypercalcemic hypercalciuria in adults, is very rare in children.[56,57] *Hypervitaminosis D* due to administration of vitamin D-containing multivitamin preparations, vitamin D added to milk preparations, or even vitamin D prophylaxis in (preterm) infants can induce hypercalcemia and hypercalciuria.[44] An excessive daily intake of *vitamin A*, $>10{,}000$ units, may lead to hypercalcemia and hypercalciuria.[58,59] Even short-term *immobilization* reduces bone mass of about 15–20% accompanied by hypercalciuria.[60]

Further reasons are long-term administration of furosemide, dexamethasone, or ACTH.[61–64] Hypercalciuria is also found in several syndromes, either linked to the pathogenesis (Bartter's syndrome,[65] Williams' syndrome[66]) or due to renal tubular damage (Wilsons' disease, Dent II syndrome;[67,68] Table 1). Further conditions include hyper- and hypothyroidism, Cushing syndrome, adrenal insufficiency and metastatic malignant bone disease, long-term assistant ventilation, ongoing acid–base changes (metabolic acidosis, reduced bone density), and long-term parenteral nutrition.[69–72]

Hyperoxaluria

Hyperoxaluria was shown to be an important promoter of crystallization.[3,70] Urinary oxalate is mostly of endogenous origin; only $\sim$10% derive from the daily nutritional intake.[73,74] Primary causes are distinguished from secondary ones.

All currently known types of *primary hyperoxaluria* (PH I–III) are rare, autosomal recessive diseases of the glyoxylate metabolism. In PH I, low or absent activity of liver-specific peroxisomal alanine:glyoxylate aminotransferase (AGT) causes massive hyperoxaluria.[75] PH I is the most frequent subtype, and the underlying *AGXT* gene comprising 11 exons is located on chromosome 2q36–37.[76] Diagnosis is mostly based on complete *AGXT* sequencing and >150 mutations have been identified throughout the gene. The disease prevalence is approximately two patients per million population.[77] The highly elevated urinary excretion of oxalate and glycolate (>1 mmol/1.73 m^2 body surface area per day, normal <0.5) causes renal calculi, medullary NC, or both[78]

(Figure 1d). With disease progression and declining renal function, calcium oxalate crystals are systemically deposited.[77,78] There is a substantial genetic, biochemical, and phenotypic heterogeneity ranging from infantile end-stage renal failure (ESRF) to a late onset or oligosymptomatic course in advanced adulthood. Unfortunately, most patients will develop ESRF over time; therefore, early diagnosis is mandatory, but is all too often delayed.[77–80]

Primary hyperoxaluria type II (PH II) seems to be even more rare (about a tenth of the PH I fraction) or remains markedly underdiagnosed. It is characterized by increased urinary excretion of oxalate and L-glyceric acid due to a defect of D-glycerate dehydrogenase and hydroxypyruvate reductase (GRHPR).[81] The *GRHPR* gene located on chromosome 9p11 is composed of 9 exons with 17 currently known causative mutations.[81] The clinical course of PH II is generally more benign, but symptoms may be clinically indistinguishable from PH I. ESRF occurs less frequently, has not been reported in childhood, but still affects about 20% of adults.[82,83]

Recently, mutations in a third, 7 exons-spanning gene (*HOGA1* (ref. 84)) on chromosome 10 were found to cause PH III.[85] *HOGA1* encodes for a mitochondrial 4-hydroxy-2-oxoglutarate aldolase. Little is known about the pathogenetic basis of PH III, but increased glyoxylate generation by activating mutations was the mechanism proposed.[85] What may be extrapolated (with due caution) from the limited data available is the fact that this subtype is about to become the second most frequent form and shows the most favorable outcome. Although PH III so far has no documented case of ESRF, initial presentation in infancy with massive uni- or bilateral nephrolithiasis eventually complicated by urinary tract infections can be quite severe.

Both the United States (Mayo Clinic Hyperoxaluria Center) and the OxalEurope PH registries contain still unclassified patients with the clinical and biochemical characteristics of PH but negative *AGXT*, *GRHPR*, and *HOGA1* analysis. Collaboration with either register is strongly encouraged and appreciated, as it will substantially aid in the identification of novel genes in the near future.

Secondary enteric hyperoxaluria

Hyperoxaluria based on increased intestinal oxalate absorption after bariatric surgery was clearly associated with stone formation. Although such procedures are (still) uncommon in children, intestinal surgery may be necessary for other reasons (e.g., necrotizing enterocolitis). Secondary hyperoxaluria of childhood is frequently found in patients with chronic inflammatory bowel disease (e.g., Crohn's) or with malabsorption syndromes (cystic fibrosis, celiac disease, a-β lipoproteinemia, Figure 1c).[86–88] Normally, oxalate is intestinally bound to calcium to form insoluble calcium oxalate, which is not absorbed. In patients with enteric hyperoxaluria, calcium instead binds to fatty acids, and thus more soluble oxalate is available for absorption.[73] Second, intestinal oxalate-degrading bacteria, e.g., *Oxalobacter formigenes,* are often not found in patients with frequent antibiotic treatment, e.g., in cystic fibrosis.[86] Up to 50% of our patients with cystic fibrosis have hyperoxaluria and around 11% develop UL or NC.[88] Importantly, enteric hyperoxaluria may also lead to severe NC and/or recurrent UL,[89] even with progression to ESRF and systemic oxalosis, especially in Crohn's disease and short bowel syndrome.[90]

Hypocitraturia

A low citrate excretion is not always adequately recognized as a risk factor in the pathogenesis of calcium-containing stones.[91] Low urinary citrate excretion is characteristic of the complete form of distal renal tubular acidosis.[92] Hypocitraturia is also observed in persistent mild or latent metabolic acidosis, in hypokalemia, and in patients with malabsorption syndromes.[88] Idiopathic hypocitraturia may be secondary to low intestinal alkali absorption.[3] Hypocitraturia is the most important risk factor for stone disease in specific regions of the world, e.g., in Turkey, and also in risk groups, e.g. preterm infants.[4,32] Therefore, urinary citrate excretion has to be determined in every patient with stones or NC.

Medication and intoxication

About 1–2% of all kidney stones are drug related.[93] Many patients with drug-induced UL, however, have additional metabolic abnormalities as risk factors.[3] Urinary excretion of poorly soluble drug components that form stones themselves or provide a nidus for stone formation is distinguished from medication increasing the excretion of lithogenic (e.g., loop diuretics, calcium/vitamin D supplementation) or reducing the excretion of inhibitory substances (carbonic-anhydrase inhibitors, topiramate), thus also being risk factors for NC. For example, hypercalciuria induced by loop diuretics was reported as one major risk factor in NC of prematurity.[64] Inhibition of carbonic anhydrase not only induces hypercalciuria but also hypocitraturia due to metabolic acidosis and an alkaline urinary pH, both leading to calcium phosphate precipitation.

Severe hyperoxaluria after intoxication with ethylene glycol, usually observed after accidental ingestion of antifreeze or because of suicide attempts, is based on the conversion to glycolic acid, formalin, and oxalic acid via alcohol dehydrogenase. This results in acute renal failure due to calcium oxalate crystal agglomeration in the renal parenchyma.[94] Diagnostic hints are an extreme anion gap and abundant calcium oxalate crystals in the urine. Treatment consists of administration of ethanol or 4-methylpyrazole to block the alcohol dehydrogenase, bicarbonate to treat the metabolic acidosis, and hemodialysis to remove both ethylene glycol and its metabolites.[94]

Tumor treatment

Recent studies deal with the prevalence of kidney stones in large cohorts of survivors of childhood acute lymphatic leukemia, with a prevalence of 0.9% of symptomatic calcifications[95] and a prevalence of 4.5% of asymptomatic

renal stones.[96] As expected, steroid treatment associated with reduced bone formation, loss of mineral from bone, and reduced intestinal and renal calcium absorption was a major determinant for stone formation or NC. Accordingly, Kaste *et al.*[96] found a negative correlation between asymptomatic renal calcifications and bone mineral density, yet without differences in serum or urinary calcium. In addition, tumor lysis syndrome leading to hyperuricosuria is implicated in stone formation in tumor patients,[97] as well as tubular damage after chemotherapy.

RISK FACTORS (UL)

Cystinuria

Cystinuria is one of the most frequent genetic disorders with an overall prevalence of 1:7000 (with data for Europe and the United States ranging from 1 in 1000 to 1 in 17,000)[98,99] and an autosomal recessive trait (Table 1). Cystinuria is the cause of up to 10% of all urinary stones in children.[100–104] More than 50% of patients develop bilateral UL, and without adequate treatment patients will suffer from recurrent stone formation.[103] The majority of patients develop their first stone during the first two decades of life.[104] Cystinuria is caused by a defective transport of cystine and the dibasic amino acids lysine, ornithine, and arginine through the epithelial cells of the renal tubule and the intestinal tract, but only cystine is insoluble enough to form stones. At pH >8, cystine solubility is increased threefold.[105] Three types of cystinuria are now distinguished according to the disease-specific genotype, with type A having the mutation on chromosome 2, type B on chromosome 19, and type AB with mutations on both chromosomes.[104] Interestingly, there is no clinical difference based on the different genotypes.

Hyperuricosuria

Uric acid stones are rarely found in children. Hyperuricosuria results from high-purine diets, myeloproliferative disorders, tumor lysis syndrome, or enzymatic defects. Many drugs, e.g., probenecid, high-dose salicylates, or contrast media, also increase uric acid excretion. However, low urine pH and low urine volume are far stronger risk factors for stone formation than hyperuricosuria *per se*.

Some rare inherited deficiencies of the purine salvage enzymes hypoxanthine-guanine-phosphoribosyltransferase (HPRT) and adenine-phosphoribosyltransferase lead to primary purine overproduction (Table 1). X-linked Lesch–Nyhan syndrome occurs in complete deficiency of HPRT. It is characterized by mental retardation, automutilation, choreoathetosis, gout, and uric acid NC.[106] Partial deficiency of HPRT results in UL and renal failure.[107] Gout and UL were also reported in glycogen storage disease type I.[108]

Deficiency of adenine-phosphoribosyltransferase results in 2.8 dihydroxyadeninuria[109] with autosomal recessive inheritance. Serum uric acid is normal and the stones are radiolucent and may be confused with uric acid. The urine contains characteristic brownish round crystals. Diagnosis is confirmed by analysis of adenine-phosphoribosyltransferase activity in red blood cells or of excretion of dihydroxyadenine in the urine.

In *xanthinuria*, serum uric acid concentration is very low because of deficiency of xanthine oxidase, which converts xanthine to uric acid (Table 1). Characteristic findings of xanthinuria are an orange-brown urinary sediment or orange-stained nappies and later xanthine stones.[110]

Urinary tract infections

Infectious stones are mainly composed of *struvite* (magnesium ammonium phosphate), but often also contain carbonate apatite, the crystallization of which is favored by a high urinary pH (>7.0). Urease-producing bacteria are responsible for the formation of struvite calculi. Urea is hydrolyzed to ammonium ions, which results in a high urinary pH. Many Gram-positive and Gram-negative bacteria produce urease. However, Proteus species are the predominant organisms.

Most struvite stones are found in the kidney (Figure 1b), but they may also form in the bladder. They are mainly seen in boys under the age of 5 years. In one-third of patients, there is a primary anomaly of the urinary tract, most often uretero–pelvic junction obstruction, primary mega-ureter, or, more rarely, ureterocele or urethral valves.[111] Patients with a neurogenic bladder, particularly those with meningomyocele, are particularly prone to struvite stones.[112] Stones may also occur during secondary infection on a nidus of different composition, e.g., cystine or calcium oxalate. It is therefore important not to miss an underlying metabolic disorder. Urine stasis increases the risk of crystallization. Stones found in patients with uretero–pelvic obstruction must therefore not necessarily be of infectious (or vice versa metabolic) origin.[113]

Medication and intoxications

UL due to melamine contamination of powdered milk formula attracted international attention in 2008 when more than 50,000 children in the Republic of China suffered from UL and acute or chronic kidney injury.[114] Children exposed to high-melamine formula displayed a 5.4- to 7.0-fold increased risk of UL. Melamine is a synthetic chemical added to milk or animal feed to boost the apparent protein content because of its high nitrogen content.[114,115] Melamine-contaminated animal food had induced stone outbreaks in cats and dogs.[116] Acute kidney injury was characterized by necrosis of distal tubular cells, mild inflammation, and intratubular green radial crystals and crystalluria. Chronic toxicity was associated with larger crystals, interstitial inflammation, and fibrosis.[115,117,118]

Indinavir, a protease inhibitor implicated in the treatment of AIDS, is excreted unchanged in the urine, leading to stone formation in 2–28% of patients including children. The stones are composed of indinavir alone or as a mixture, with indinavir as nidus for calcium-containing stone formation. As indinavir is poorly soluble at pH >5, urinary acidification, increased fluid intake, and, if possible, discontinuation

of therapy may dissolve stones.[119–124] Other medications precipitating in the urine but rarely causing stones include ceftriaxone, sulfonamides, ampicillin, amoxicillin, triamteren, acyclovir, and oxypurine.

RISK FACTORS (NC)

Prematurity

Several studies have analyzed factors contributing to the increased prevalence of NC in preterm infants. Because of heterogeneous study settings[125] and a moderate inter- and intra-observer variation of ultrasound results, a wide range of prevalence rates (7–64%) were found.[126–135] However, the more recent studies[126,127,133–135] report a lower, but nevertheless high prevalence rate (7–41%).

Nephrogenesis is not complete until 34–36 weeks of gestational age, and hence the immature renal epithelium could be a major factor facilitating crystal retention.[39] In addition, premature kidneys have a long loop of Henle and hence a low urine velocity,[125] resulting in crystal aggregation in the tubules. In fact, NC has been clearly associated with low gestational age and birth weight.[127–130,133,136,137] Gimpel *et al.*[136] found a 1.65-fold increased risk per 100 g lower birth weight. In this study, furosemide therapy with >10 mg/kg body weight per day was the strongest independent risk factor increasing the risk of NC about the factor 48. Whereas some studies identified furosemide therapy as a major risk factor,[127,133,137] others did not.[134] The reduction of passive calcium reabsorption normally driven by sodium chloride transport leads to hypercalciuria and may be aggravated by a slower plasma clearance.[138,139] Hypercalciuria itself was reported to increase the risk of NC about 4.5 times per mmol/l increase of urinary calcium concentration.[136] Hypercalcuria in preterm infants has also been associated with high-dose steroid treatment,[133,137,140] whereas other studies did not identify this as an independent risk factor.[136] In particular, in very low birth weight infants (<1000 g), hypocitraturia was identified as the major risk factor,[137,141] and high intake of calcium, phosphorus, and ascorbic acid were also reported to contribute to renal calcification in preterm neonates,[137] as well as gentamicin therapy.[133] Interestingly, genetic factors also seem to have a role, as neonates with a positive family history of kidney stones, those of male gender, and those of Caucasian race are more likely to develop NC.[132,133]

Spontaneous resolution over time in the majority of preterm infants was reported in recent long-term studies.[131,141–145] A prospective observational study revealed a 35% probability of NC present at term to persist for at least 15 months and a 15% probability to persist for at least 30 months.[145] A persistence rate of 10–25% was reported after 7.5 years.[143,144] However, all data rely on repeated ultrasound examinations, whereas true resolution might only be proved by other imaging methods or kidney biopsy. No difference in renal function, expressed as glomerular filtration rate levels, was found at a mean age of 4.7,[146] 3–6 years[127,] and 5.8–7.7 years.[143] It is noteworthy that prematurity itself can lead to impaired glomerular filtration rate.[143,147]

Kidney transplantation

A high prevalence (2–60%) of renal calcifications was reported in renal transplant patients. Detection rates were profoundly dependent on the diagnostic procedures.[49,148–151] Hypocitraturia and the immunosuppressive (nephrotoxic) treatment *per se* were reported as risk factors;[149,150] however, there is dispute about its impact on allograft function over time. The high prevalence (27%) of renal calcification in patients with delayed graft function[152] might be the consequence of more severe acute tubular necrosis. Pinheiro *et al.*[153] reported a worse long-term patient, as well as allograft, survival in those with allograft calcifications present 3 months after transplantation. However, long-term studies are clearly needed to elucidate the impact of calcifications on allograft function.

CLINICAL PRESENTATION AND DIAGNOSTIC PATHWAY

UL/NC are only the symptom of underlying diseases but not the disease itself. Thus, a thorough diagnostic evaluation is required in each child[4,154] to start specific treatment as early as possible. Medical history should include all possible information about prematurity, concomitant diseases, fluid intake, diet, vitamin supplementation, and medical treatment. A thorough family history provides information about potential genetic disorders (see Table 1).

The interpretation of clinical symptoms might be difficult, especially in younger children. Analogous to adults, most children present with flank or abdominal pain.[1,19,155] However, atypical and nonspecific complaints are more likely in younger children, especially in those who are not yet able to articulate their complaints.[4,14] A history of UL, nausea, and vomiting, the presence of flank pain, or more than two red blood cells per high power field in urine microscopy were all positively associated with childhood UL.[6] NC is mostly asymptomatic and often only diagnosed when ultrasound is performed for other reasons. Very frequently, gross or microscopic hematuria and/or sterile leukocyturia are misinterpreted as urinary tract infection.[11]

The 24-h urine analysis of lithogenic and stone inhibitory parameters should be regarded as gold standard, although in the smaller infant spot urine evaluations might only be possible (Table 2). Diagnostic imaging is first provided by ultrasound of the kidneys, ureters, and bladder. Even if stones are not visible on ultrasound (due to overlying with bony structures), a secondary phenomenon due to obstruction can be visualized. Unenhanced CT of the abdomen depicts stones more accurately compared with ultrasound also in pediatric populations.[156–158] It is worth mentioning that ultrasound detects 90% of kidney stones, but only 38% of ureteral stones compared with CT.[157] However, in infants and young children, minimization of exposure to ionizing irradiation and the need for sedation to perform a CT favor the use of ultrasonography over CT.

TREATMENT

Acute management (UL)

Patients with NC do not normally present with acute symptoms.[4,44] In contrast, patients with acute renal colic

Table 2 | Normal values for lithogenic and stone-inhibitory parameters in spot urine (related to creatinine excretion) and 24-h urine collection (tubes or container need to be preserved with either thymol 5% in isopropanol, or 2 N Hcl before collection starts)

Calcium/creatinine		Citrate/creatinine			Cystine/creatinine			Oxalate/creatinine			Urate/creatinine		
mol/mol	g/g		mol/mol	g/g		mmol/mol	mg/g		mmol/mol	mg/g		mol/mol	g/g
Soluble/creatinine ratio (spot urine samples)													
< 12 Months	< 2.2	< 0.8	0–5 Years	> 0.12 to 0.25	> 0.2 to 0.42	< 1 Month	< 85	< 180	0-6 Months	< 325 to 360	< 260 to 88	< 12 Months	< 1.5	< 2.2
1–3 Years	< 1.5	< 0.53							7–24 Months	< 132 to 174	< 110 to 39	1–3 Years	< 1.3	< 1.9
3–5 Years	< 1.1	< 0.4	> 5 Years	> 0.08 to 0.15	> 0.14 to 0.25	1–6 Months	< 53	< 112	2–5 Years	< 98 to 101	< 80 to 81	3–5 Years	< 1.0	< 1.5
5–7 Years	< 0.8	< 0.3							5–14 Years	< 70 to 82	< 60 to 65	5–10 Years	< 0.6	< 0.9
> 7 Years	< 0.6	< 0.21				> 6 Months	< 18	< 38	> 14 Years	< 40	< 32	> 10 Years	< 0.4	< 0.6
Urinary excretion of soluble in 24-h urine samples														
Calcium excretion		Citrate excretion			Cystine excretion			Oxalate excretion			Urate excretion		
All age groups	< 0.1 mmol/kg per 24 h < 4 mg/kg per 24 h	All age groups	*Boys*: > 1.9 mmol/1.73 m^2 per 24 h > 365 mg/1.73 m^2 per 24 h *Girls*: > 1.6 mmol/1.73 m^2 per 24 h > 310 mg/1.73 m^2 per 24 h		< 10 Years > 10 Years	< 55 mmol/1.73 m^2 per 24 h < 13 mg/1.73 m^2 per 24 h < 200 mmol/1.73 m^2 per 24 h < 48 mg per 1.73 m^2 per 24 h		All age groups	< 0.5 mmol/1.73 m^2 per 24 h < 45 mg/1.73 m^2 per 24 h		< 1 Year 1–5 Years > 5 Years	< 70 mmol/kg per 24 h < 1.3 mg/kg per 24 h < 65 mmol/kg per 24 h < 1.1 mg/kg per 24 h < 55 mmol/kg per 24 h < 0.9 mg/kg per 24 h	

Repeat collection after stone passage or removal, as stones *in situ* may diminish lithogenic excretion parameters. Check 24-h urine volume and creatinine excretion (2 mg/kg ± 0.8 mg) to ensure adequate collection.

due to stones present with severe pain, and thus analgetic treatment has to be initiated directly and in an adequate dosage. Calcium channel blockers, α-blockers, and corticosteroids were shown to induce stone passage.[159] Further management depends on the (ultrasound) evidence of obstruction due to the stone. In case of persisting obstruction, impairment of renal function (e.g., due to bilateral obstruction), or of an acute infection (e.g., pyuria), prompt removal of the stone is indicated. Initial urine drainage by nephrostomy tube might be performed to facilitate urine excretion and to avoid further kidney damage. In the absence of obstruction, large fluid administration combined with ongoing application of analgetics, α or calcium channel blockers combined with steroids is indicated to induce stone passage.[160]

Chronic management

Prevention is the main and most important therapeutic goal! Management of children with NC/UL is mainly based on the reduction of the solute concentration in the urine. Independently of the underlying disorder, a high fluid intake (> 1.5 to 2 l/1.73m^2 body surface area per day) is the precondition for all further treatments. Fluid intake is distributed over the whole day providing a stable urinary excretion rate and avoiding peaks of high concentration levels of the lithogenic substance. Dietary recommendations have to be carefully handled. A low calcium diet in calcium stone formers should be avoided, as it may lead to secondary hyperoxaluria. However, also a low oxalate diet in those patients with secondary hyperoxaluria should be restricted to food with a very high oxalate content, in order to avoid disturbances of the intestinal interplay of ions resulting in increased intestinal calcium absorption. An increase in potassium intake and a decrease in sodium intake can be recommended, but is often difficult to realize in children.[161]

Apart from high fluid intake, crystallization inhibitors—mainly citrate and magnesium—are an effective treatment option. Citrate is metabolized in the liver to bicarbonate, resulting in a higher urinary pH and therefore reduced citrate reabsorption in the renal tubule. Urinary citrate binds to calcium, forms a soluble complex reducing the precipitation of calcium with other substances, thus leading to a decreased urinary saturation index. Urinary calcium excretion can be reduced by 30% with adequate alkali citrate treatment. Alkali citrate has been shown to decrease stone production and reduce progression of NC[162,163] (personal experiences). The recommended daily dosage of alkali citrate is 0.1–0.2 g/kg body weight (0.3–0.6 mmol/kg body weight) in a sodium potassium or, best, potassium citrate preparation. In patients with distal RTA, the dosage has to be adapted to the serum pH and can be given completely as potassium-based solution. In these children, a minimal dosage of 0.2–0.3 g/kg body weight is often needed.[69] Urine alkalinization increases the solubility of cystine, uric acid, and calcium oxalate. However, urinary pH should be monitored, as very high pH levels carry the risk of calcium phosphate precipitation.

Severe hypercalciuria is treated with thiazides. They reduce renal calcium excretion by increasing calcium uptake in the distal tubule and stimulate calcium reabsorption in the proximal tubule via volume control. In particular, in children with reduced bone density due to hypercalciuria, thiazide treatment is indicated, as it may improve bone density. A daily dosage of 0.5–1 mg/kg body weight (hydrochlorothiazide) is given b.i.d., but side effects such as hypokalemia and hypotension have to be considered. Here, amiloride as additional calcium-lowering but potassium-sparing medication should be added.[164]

Patients with PH I are treated with pyridoxal phosphate, a disease-specific chaperone medication (cofactor of the defective enzyme). Treatment in supra-physiological doses (5–20 mg/kg body weight per day, stepwise increase by 5 mg/kg body weight) helps to reduce the endogenous oxalate production and hence the urinary oxalate excretion in approximately a third of patients.[79] Noteworthy side effects are polyneuropathy, but sometimes bullous skin eruptions as well.

Future treatment options in patients with all types of PH might include oral administration of intestinal oxalate-degrading bacteria, e.g., *Oxalobacter formigenes*. Oral *oxalobacter* administration was found to be effective in two pilot trials.[165] A recent multicenter trial, however, was unable to reproduce the striking results in general. Nevertheless, '*ad hoc*' analyses of a subset of truly compliant patients suggested an effect when urine oxalate was analyzed by oxalate to creatinine ratio.[166] Next to that, but now in patients with secondary hyperoxaluria, the oral administration of oxalate-degrading enzymes might help reduce the dietary oxalate burden, and thus prevent elevated intestinal oxalate absorption.

Patients with PH and ESRF should be transplanted as early as possible, as no renal replacement therapy is capable of removing sufficient amounts of oxalate. Combined liver–kidney transplantation is performed in patients with PH I to cure the liver-specific enzyme defect. In addition, preemptive liver transplantation was performed, but timing of the procedure is difficult because of the clinical heterogeneity of the disease. Future transplantation options might include hepatocyte transplantation as a bridging procedure before combined transplantation, especially in patients with infantile oxalosis. Isolated kidney transplantation is performed in PH II (the defective enzyme is ubiquitous).

A methionine-restricted diet may be recommended in patients with cystinuria, as it is metabolized to cystine within the organism. Methionine is found in protein-rich food; however, strict protein restriction is not recommended in children[105] and mild protein restriction is difficult to achieve even in adolescents and adults. Because of the higher solubility of cystine at urinary pH >8, urine alkalinization is the main goal of pharmacotherapy. In addition, chelating agents that cleave the disulfide bond of cystine to cysteine, a homodimer of cystine, which is 50 times more soluble, will be administered. D-penicillamine and α-mercaptopropionyl-glycine are equally effective and used in a dosage of 20–40 mg/kg body weight per day b.i.d. Side effects occurring in 20–50% of patients including rash, arthralgia, exanthema, thrombocytopenia, polymyositis, and nephritic syndrome limit treatment. It is noteworthy that D-penicillamine reduces the level of pyridoxine, which therefore has to be supplemented.[104] Ascorbic acid can reduce cystine to cysteine when administered in very high doses; however, there is ongoing debate about the efficacy.[167,168] As high ascorbic acid levels can increase the endogenous oxalate production and hence urinary oxalate excretion, this therapy should be avoided in patients at risk for calcium oxalate stone formation.

Moreover, in patients with purine stones (uric acid, 2,8-dihydroxyadenine, xanthine), high fluid intake and urine akalinization to maintain a urinary pH above 6.5 are the main goals. Protein excess has to be avoided to reduce purine intake. In cases of refractory hyperuricosuria, allopurinol (inhibitor of the xathine-oxidase) can be given. Here, careful dosing regimens are necessary, as allopurinol treatment may lead to significant xanthinuria. In contrast to uric acid, xanthine solubility does not increase in alkalinized urine, and thus citrate is of no effect and fluid intake is the main means of therapy.[110] In patients with 2,8-dihydroxyadenine stones, urine dilution and allopurinol are, besides dietary restrictions of adenine and purine, the only therapeutic measures.

Finally, in children with (recurrent) infectious stones, stone removal and surgical management of a possible anatomic anomaly are necessary. If stones remain *in situ*, the next urinary tract infection will occur after antibiotic treatment is ceased, as the stone functions as nidus for bacterial growth.

CONCLUSION

The incidence of UL and NC seems to also increase in children and adolescents. Children with kidney stones or NC, however, should not be treated like adults. They have to be carefully examined to unravel the genetic or metabolic background and to prescribe a proper preventive treatment. It is recommendable that specialized pediatric centers take care of children with rare (metabolic) diseases leading to recurrent kidney stones.

DISCLOSURE

All the authors declared no competing interests.

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