Nephrolithiasis in children in 2023

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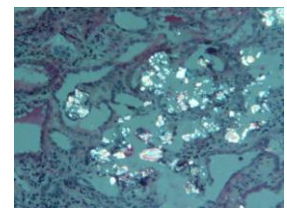
Epidemiology and pathophysiology of pediatric lithiasis



Pediatric lithiasis: not a myth!

- **10-15% of general population**
  - At least one lithiasis during life
- 30 times more frequent in adults

- **But children can also be affected**
  - Atypical symptoms in the youngest children, UTI as first symptoms in 16%, 50% familial history
  - 162 children (2 months – 16 years, mean 5.6±0.4, 78 girls)

Presenting symptoms	Age of patient at presentation		
	<1 year	1–5 years	>5 years
Hematuria	9 (13.4%)	11 (36.7%)	15 (23.8)
Flank pain or restlessness	11 (16.4%)	4 (13.3%)	26 (41.3%)
UTI	18 (26.9%)	4 (13.3%)	4 (6.3%)
Incidentally discovered	20 (29.9%)	6 (20%)	12 (19%)
Other	9 (13.4%)	5 (16.6%)	6 (9.5%)
Total	67	30	63

Alpay Pediatr Nephrol 2009

Genetic causes, but not only…

Table 2 Urinary metabolic examination of study group

Metabolic evaluation	Percentage[a]
Hypercalciuria	33.8
Hypocitraturia	33.1
Hyperoxaluria	26.5
Hyperuricosuria	25.4
Hypocitraturia + hypercalciuria	21.1
Hyperphosphaturia	20.8
Cystinuria	5.7
Normal metabolic examination	13.1

[a] Percentage of patients with positive test results among all studied subjects. In some patients more than one test was positive

Alpay Pediatr Nephrol 2009

Pathophysiology of lithiasis is complex

- Metabolic abnormalities
- Genetic factors
- Environment: nutrition ++++
- Uropathies
- UTI
- Etc, etc

Lithiasis = an imbalance

Promoting factors	*Inhibiting factors*
Calcium	Citrate
Oxalate	Magnésium
Acide urique	Phosphate
Cystine	Protéines
Médicaments	Uropontine
Débris cellulaires	Néphrocalcine
Nanobactéries	Uromoduline

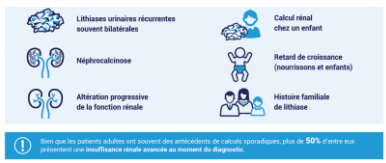
Volume et pH des urines

- *pH < 5.3: low solubility: uric acid, cystine, xanthine*
- *pH>6.5: PhxCa, PAM*

When thinking of a genetic cause of lithiasis?

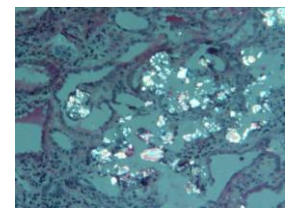
Tableau 65.3 Maladies héréditaires responsables de lithiases : éléments d'orientation

- Début souvent précoce
- Antécédents familiaux de lithiases rénales
- Consanguinité parentale
- Calculs bilatéraux et multiples
- Récidives fréquentes (50 % à 5 ans)
- Néphrocalcinose souvent associée
- Atteinte tubulaire :
  - syndrome clinique : polyurodipsie, retard statural
  - syndrome biologique : acidose métabolique, trouble de concentration
- Parfois signes extrarénaux spécifiques

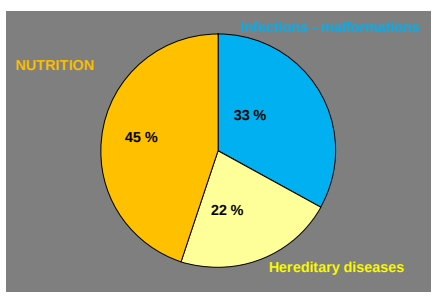


Bien que les patients adultes ont souvent des antécédents de calculs sporadiques, plus de **50%** d'entre eux présentent une **insuffisance rénale avancée au moment du diagnostic**.

Etiologies of pediatric urolithiasis



Pediatric lithiasis

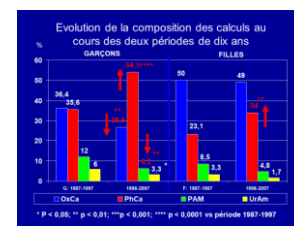


Evolution of lithiasis type with time

Data from Pr Daudon, Necker, 1579 stones between 1987 and 2007
Ratio M/F = 2.04
Age : G = 6,3 ± 5,4 years - F = 9,4 ± 5,5 years

- **Decreased UTI-induced**
- **Increased Ca-dependent lithiasis in both genders**

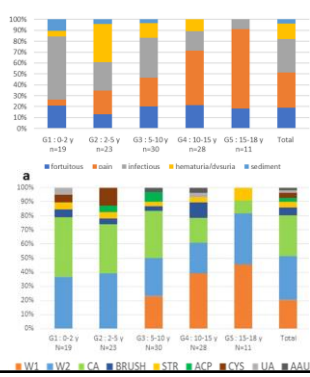
- **Changes in medical management**
- **Changes in nutrition +++**



Stechmann Pediatr Nephrol 2009

Composition of urinary stones in children: clinical and metabolic determinants in a French tertiary care center

Inclusion: FTIR of the lithiasis in Lyon between 2013-2,17; N=111 patients



- Decreased UTI-induced (22%)
- Mainly Ca lithiasis

- Metabolic abnormalities found in 50% of the 70 patients tested
  - 19% hyperCaU
  - 14% hyperOxU
  - 7% Hypocitraturia

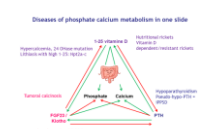
- Some patients were still not referred to ped-nephrologists…

- CAKUT and neurological bladder: a risk factor for lithiasis, but rule out other risk factors

Rauturier, EJP 2021

Classification of hereditary lithiasis

- **Proximal tubulopathies**
  - Dent disease
- **Distal and collecting duct tubulopathies**
  - Bartter
  - Hypomagnesemia and hyperCaU (claudin)
  - Distal tubular acidosis
  - Pseudohypoaldosteronism type 2
- **Other monogenic diseases**
  - Cystinuria (1 / 20 000)
  - Hyperoxaluria (1 / 120 000)
  - Purine diseases (xanthine / dihydroxy 2,8 adenin)
- **Abnormalities of phosphate/calcium metabolism**
  - Vitamin D
  - PTH
  - FGF23



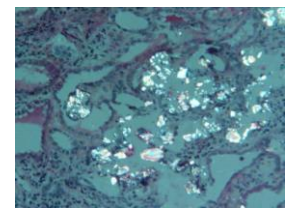
Hereditary lithiasis and hypercalciuria

Table 1 Genetic defects associated with some monogenic forms of hypercalciuria

Disease[a]	Mode of inheritance[b]	Gene[c]	Human chromosomal location	Reference
Idiopathic hypercalciuria				
	A-d	SAC	1q23.3-q24	[35]
	A-d	VDR	12q12-q14	[30]
	A-d	?	9q33.2-q34.2	[31]
ADHH	A-d	CASR	3q21.1	[40]
Hypercalcemia with hypercalciuria	A-d	CASR	3q21.1	[38]
Bartter syndromes				
Type I	A-r	SLC12A1/NKCC2	15q15-q21.1	[90]
Type II	A-r	KCNJ1/ROMK	11q24	[91]
Type III[d]	A-r	CLCNKB	1q36	[92]
Type IV[d]	A-r	BSND	1q31	[93]
Type V	A-d	CASR	3q21.1	[48]
Type VI[e]	X-r	CLCN5	Xp11.22	[50]
Dent's disease	X-r	CLCN5	Xp11.22	[52]
Lowe's syndrome	X-r	OCRL1	Xq25	[60]
HHRH	A-r	NPT2c/SLC34A3	9q34	[69]
Nephrolithiasis, osteoporosis and hypophosphatemia	A-d	NPT2a/SLC34A1	5q35	[64]
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	A-r	PCLN1/CLDN16	3q28	[73]
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular abnormalities	A-r	CLDN19	1p34.2	[77]
dRTA	A-d	SLC4A1/kAE1	17q21.31	[81]
dRTA with sensorineural deafness	A-r	ATP6B1/ATP6V1B1	2p13	[85]
dRTA with preserved hearing	A-r	ATP6N1B/ATP6V0A4	7q34	[88]

Stechmann Pediatr Nephrol 2009

Evaluation of a lithiasis in pediatrics



Medical history

- **Familial history**
  - Consanguinity
  - Lithiasis, deafness
  - CKD, dialysis
- **Croissance staturo-pondérale, polyuro-polydypsie**
- **Nutrition: dairy products, calcium, sodium and proteins +++**
- **Vitamin D supplementation (drug and unlicensed vitamin D « over the counter »)**
- Treatment
- Past of UTI or unexplained fever

Reference values
Matos, Journal of Pediatrics 1997

	P/Cr U mol/mol (mg/mg) *		Ca/Cr U mol/mol (mg/mg) *		Mg/Cr U mol/mol (mg/mg) *	
Age (ans)	5ème p	95ème p	5ème p	95ème p	5ème p	95ème p
< 1	1.2 (0.34)	19.0 (5.24)	0.09 (0.03)	2.2 (0.81)	0.4 (0.10)	2.2 (0.48)
1-2	1.2 (0.34)	14.0 (3.95)	0.07 (0.03)	1.5 (0.56)	0.4 (0.09)	1.7 (0.37)
2-3	1.2 (0.34)	12.0 (3.13)	0.06 (0.02)	1.4 (0.50)	0.3 (0.07)	1.6 (0.34)
3-5	1.2 (0.33)	8.0 (2.17)	0.05 (0.02)	1.1 (0.41)	0.3 (0.07)	1.3 (0.29)
5-7	1.2 (0.33)	5.0 (1.49)	0.04 (0.01)	0.8 (0.30)	0.3 (0.06)	1.0 (0.21)
7-10	1.2 (0.32)	3.6 (0.97)	0.04 (0.01)	0.7 (0.25)	0.3 (0.05)	0.9 (0.18)
10-14	0.8 (0.22)	3.2 (0.86)	0.04 (0.01)	0.7 (0.24)	0.2 (0.05)	0.7 (0.15)
14-17	0.8 (0.21)	2.7 (0.75)	0.04 (0.01)	0.7 (0.24)	0.2 (0.05)	0.6 (0.13)

Reference values *Slev, Pediatr Nephrol 2010*

Age group (years)	Girls			Boys			Boys and girls	
	Central 95% reference interval	Upper limit 90% confidence interval	Number of samples	Central 95% reference interval	Upper limit 90% confidence interval	Number of samples	Central 95% reference interval	Upper limit 90% confidence interval
Calcium (mg/mg)								
7–9	0.01–0.46	0.34–0.78	148	0.01–0.43	0.37–0.60	178	0.01–0.43	0.37–0.53
10–12	0.01–0.31	0.28–0.40	154	0.01–0.30	0.27–0.32	177	0.01–0.30	0.28–0.32
13–15	0.01–0.31	0.27–0.36	165	0.01–0.29	0.25–0.31	180	0.01–0.30	0.28–0.31
16,17	0.02–0.27	0.23–0.33	136	0.01–0.26	0.24–0.34	123	0.01–0.27	0.24–0.31
Phosphorus (mg/mg)								
7–9	0.15–1.44	1.26–1.63	147	0.17–1.68	1.43–2.08	179	0.173–1.88	1.54–2.14
10–12	0.14–1.32	1.15–1.46	153	0.14–1.23	1.10–1.35	176	0.145–1.28	1.16–1.34
13–15	0.08–0.93	0.87–1.04	164	0.10–1.13	1.00–1.48	177	0.100–1.03	0.94–1.15
16,17	0.06–0.85	0.75–1.00	133	0.07–0.87	0.75–1.23	123	0.069–0.86	0.78–0.94
Total protein (mg/mg)								
7–9	0.07–0.30	0.26–0.34	140	0.06–0.22	0.19–0.30	180	0.06–0.28	0.25–0.30
10–12	0.06–0.34	0.27–0.43	151	0.06–0.22	0.17–0.28	172	0.06–0.28	0.24–0.33
13–15	0.03–0.31	0.23–0.39	162	0.04–0.26	0.20–0.38	173	0.04–0.29	0.23–0.37
16,17	0.04–0.31	0.21–0.35	134	0.03–0.19	0.11–0.28	120	0.03–0.27	0.20–0.32

1 mg/dL = 0.25 mmol/L calcium
1 mg/dL = 88.4 µmol/L creatinine

Reference values *Cameron, Pediatr Nephrol 2005*

Table 1 Normal urinary values for children [2,5]

Normal 24-h urine values	
Calcium	< 4 mg/kg/day ou 0,12-0,15 mmol/kg/j
Oxalate	< 40 mg/1.73 m^2/day
Uric acid	< 815 mg/1.73 m^2/day
Citrate	> 400 mg/g creatinine
Cystine	< 75 mg/1.73 m^2/day
Total volume	> 20 ml/kg/day
Normal spot urine values	
Calcium/creatinine child	< 0.21 mg/mg
Infants	< 0.6 mg/mg
Oxalate/creatinine child > 4 years	< 0.1 mg/mg
Infant < 6 months	< 0.3 mg/mg
Children <4 years	< 0.15 mg/mg
Uric acid	< 0.53 mg/dl GFR
Citrate/creatinine	> 0.51 g/g

Urinary calcium and protein intake and sodium intake…

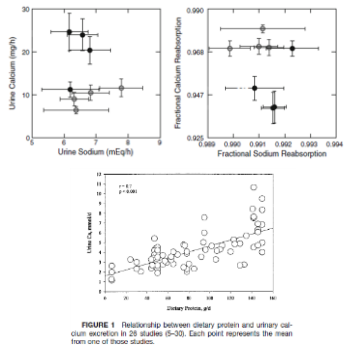


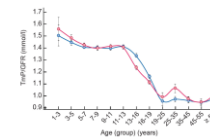
FIGURE 1 Relationship between dietary protein and urinary calcium excretion in 28 studies (5–30). Each point represents the mean from one of those studies.

Worcester, Am J Physiol Renal Physiol 2007 *Kerstetter J Nutr 2003*

Urine analysis on spot

- **Creatinuria**
- Low in neonates
- **Calciuria**
  - Absolute (concentration) hypercalciuria : Ca > 3.8 mmol/L
  - Hypercalciuria : Ca/creat U
- **Phosphaturia**
  - TmP/GFR calculation
  - TmP/GFR = Pp - [Pu x Crp / CrU]
  - In case of hypophosphatemia

Références	Age (ans)	TmP/DFG (mmol/l)	
Nourrisson	Nouveau-né	1,43–3,43	
	3 mois	1,48–3,30	
	6 mois	1,15–2,60	
Enfant	2–15	1,15–2,44	
Adulte	25–35	1,00–1,35	0,96–1,44
	45–55	0,00–1,35	0,88–1,42
	65–75	0,80–1,35	



Age (ans)	Ca/Cr U mol/mol (mg/mg) * 5ème p	95ème p
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1-2	0.07 (0.03)	1.5 (0.56)
2-3	0.06 (0.02)	1.4 (0.50)
3-5	0.05 (0.02)	1.1 (0.41)
5-7	0.04 (0.01)	0.8 (0.30)
7-10	0.04 (0.01)	0.7 (0.25)
10-14	0.04 (0.01)	0.7 (0.24)
14-17	0.04 (0.01)	0.7 (0.24)

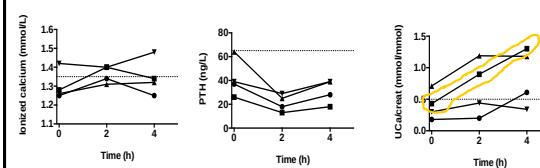
Matos J Pediatr 1997 / Derain-Dubourg NDT

24 hour urinary collection is a key assessment in children

- **Volume**
- **Creatinuria**
- Normal 0.15 mmol/kg/jour girl et 0.15-0.18 boy
- To assess the fiability of the collection
- **Calciuria**
  - Normal < 0.12 mmol/kg/day (adult 0,1)
  - Absolute (concentration) hypercalciuria : Ca > 3.8 mmol/L
  - Hypercalciuria : Ca/creat U
  - Beware of protein and sodium intake…
- **Urinary sodium**
  - mmol/24 hours
  - Divided by 17 (1g = 17 mmol…)
  - Sodium intake in g / day (target = 6)
- **Urinary urea**
  - mmol/24 hours
  - Divided by 5 and by body weight
  - Protein intake: g/kg/day

Age	Apports protéiques (g/day)	Calcium (mg/day)	Sodium (mmol/day)
0-12 months	8-10	210-270	5 de 0 à 6 mois et 16 de 7 à 12 mois
2 yrs	10-12	500	42
3 yrs	12	500	42
4-6 yrs	15-18	400-600	79
7-9 yrs	20-24	700-900	110
10-12 yrs	27-31	1000-1200	110
13-15 yrs	36-47	1200	110
16-18 yrs	50 chez le garçon et 44 chez la fille	1200	110

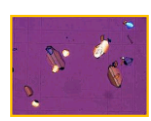
Oral calcium load: for diagnosis and education…



Mosca M, J Pediatr Urol 2020

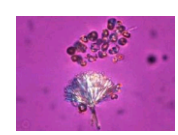
Crystalluria and stone analysis are also very important!

PO_4-NH_3-Mg (struvite, PAM)	Infection urinaire
Phosphate de calcium	Hypercalciurie
Oxalate de calcium	Hypercalciurie (wheddellite, DH)
	Hyperoxalurie (whewellite, MH)
Cystine	Cystinurie
Urate	Anomalie purines
	Hyperuricosurie
2,8 dihydroxyadénine	Déficit APRT
Xanthine	Xanthinurie



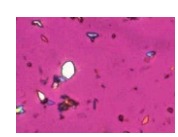
Drug-induced lithiasis

Amoxicilline



Sulfadiazine

Indinavir



Bactrim

Imaging of pediatric lithiasis: to avoid uncessary radiation exposure!

Table 2 Etiologies of secondary pediatric urolithiasis with imaging findings

Secondary urolithiasis	Etiologies	Stone contents	Imaging findings
With hypercalciuria	Dietary factors - High intake of sodium - Animal protein-rich diet - High fructose intake	Calcium oxalate	Radiopaque urolithiasis
With hyperoxaluria	Increasing intestinal oxalate absorption - Short bowel syndrome - Bariatric surgery - Exocrine pancreatic insufficiency - Crohn disease	Calcium oxalate	Radiopaque urolithiasis
Infections	Bacteria with urease activity - *Proteus mirabilis* - *Klebsiella pneumoniae* - *Pseudomonas* - *Staphylococcus aureus* - *Streptococcus pneumoniae*	Struvite or Carbapatite	Coral struvite lithiasis (Fig. 9)
Iatrogenic	Loop diuretics Vitamin D Vitamin C	Carbapatite	Radiopaque urolithiasis
Congenital abnormalities of kidney and urinary tract	- Ureteropelvic junction obstruction - Neurogenic bladder - Horseshoe kidney - Obstructive renal dysplasia	Struvite or Carbapatite	Coral struvite lithiasis Bladder stones

Bernador, Pediatric Radiology 2022

Imaging of pediatric lithiasis

Table 3 Monogenic etiologies of pediatric urolithiasis with imaging findings

Monogenic causes	Etiologies	Stone contents	Imaging findings
With hypercalciuria	Primary hyperparathyroidism	Calcium oxalate	Radiopaque urolithiasis Nephrocalcinosis
	- Variants in 24 hydroxylase gene - Variants in renal phosphate transporter NPT2a - Variants in renal phosphate transporter NPT2c	Calcium oxalate	Radiopaque urolithiasis Nephrocalcinosis Prenatal hyperechogenic kidneys
	Tubular disorders - Renal Fanconi syndrome - Dent disease - Lowe disease - Fanconi–Bickel syndrome - Types I-II-IV-V Bartter syndrome	Calcium oxalate	Radiopaque urolithiasis Nephrocalcinosis
Cystinuria	- Type 1 - Type 2	Cystine	Radiopaque urolithiasis (Fig. 10) Antenatal hyperechoic colon
Distal renal tubular acidosis	Genetic abnormality: 80% of cases	Calcium phosphate	Radiopaque urolithiasis (Fig. 11) Nephrocalcinosis Renal cysts
Hyperoxaluria	- Type 1 - Type 2 - Type 3	Calcium oxalate	Radiopaque urolithiasis (Fig. 12) Nephrocalcinosis
Purine metabolism disorders	- Hypoxanthine–guanine phosphoribosyltransferase deficiency - Phosphoribosylpyrophosphate synthetase hyperactivity - Hereditary xanthinuria	Uric acid	Radiolucent urolithiasis

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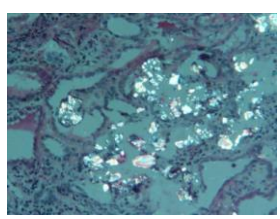
Management of pediatric urolithiasis



Global management

- Hydration, hydration, hydration
- 2-3 L/m² per day
- **To explain, sometimes the only « treatment »+++**
- Enteral nutrition may be required in the youngest

- Increase water intake
- Increase potassium intake (veggies and fruits)
- Decrease sodium and protein intake
- Normal calcium intake +++

- Prevention and early treatment of UTI
- Vitamine D as daily doses????
- If ncessary non-invasive or minimally invasive procedures

More specific management

- Potassium citrate
- 1 citron = 47 gr/L de citrate (1 citron donne 60-80 ml soit 2.5-3gr de citrate)
- 100 à 150 mg/kg/j en 3-4 doses
- Toxicité gastrique +++ : à prendre avec une quantité importante d'eau ou à mettre directement dans l'eau de boisson de la journée

- Thiazides: beware hypoK, growth retardation and theorical risk of skin cancer?

More specific management (focus on cystinuria)

- Potassium citrate: 1 citron =
- Thiazides: beware hypoK, growth retardation and theorical risk of skin cancer?

- Cystinuria: high fluid intake, low sodium diet, reduced methionine intake, urine alkalinization to increase cystine solubility, through a stepwise strategy, thiol derivatives for refractory cases, this last step having the potential to induce severe side effects, target pH-U 7.5-8.0

Table 3 | Methionine content of several foods

Food item	Content (mg/100 g)
Dried cod	2300
Horse meat	1300
Crayfish	1000
Sardines in oil	740
Tuna in oil	680
Other fish	600
Liver	600
Poultry meat	550–620
Other meat (pork, beef, mutton, and veal)	400–550
Parmesan cheese	930
Gruyère cheese	900
Emmental cheese	790
Other cheese	500–600
Eggs	390

Modified with permission from Bouzidi H, Daudon M. [Cystinuria: from diagnosis to follow-up]. *Ann Biol Clin (Paris)*. 2007;65:473–481 [in French].[21]

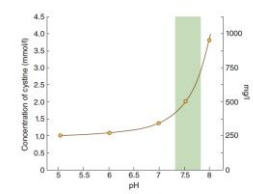


Figure 1 | Cystine solubility according to urinary pH. Adapted with permission from Bouzidi H, Daudon M. [Cystinuria: from diagnosis to follow-up]. *Ann Biol Clin (Paris)*. 2007;65:473–481 [in French].[21]

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