Urolithiasis and nephrocalcinosis in children.

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Terminology

- **Nephrolithiasis** – formation and localization of stones in the kidney
- **Urolithiasis** – stones in the kidney and anywhere in urinary tract
- **Nephrocalcinosis** – deposition of calcium in renal tubuli and interstitium
Stone surgery

Lithotomist

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Epidemiology

- Incidence 1:1000 per year (adults)
- Children 1-2 per 1000000 per year
- Peak onset 20 - 35 years of age
- Male:Female 3 - 4 : 1 (children 3:2)
- In their lifetime
  2 - 5% of the Asian population
  8 - 15% of North Americans and Europeans will form stones
- Up to 20% of stone formers have family history of urolithiasis

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M. Lopes, B. Hoppe, 2008
A. Trinchieri, 2008
Urolithiasis recurrence rate

- 40% in 2 - 3 years
- 55% in 5 - 7 years
- 75% in 7 - 10 years
- 100% in 15 - 20 years
Patophysiology of stone formation

- Urine hypersaturation
- Crystal nucleation (nidus)
- Crystal aggregation
- Stone growth
Inhibitors & Promoters of Stone Formation in Urine

INHIBITORS
Inhibits crystal Growth -
• Citrate – complexes with Ca
• Magnesium – complexes with oxalates
• Pyrophosphate - complexes with Ca
• Zinc

Inhibits crystal Aggregation
• Glycosaminoglycans
• Nephrocalcin
• Tamm- Horsfall Protein
  – Oxalobacter (gut)

PROMOTERS
• Bacterial Infection
• Anatomic Abnormalities – PUJ obst., MSK
• Altered Ca and oxalate transport in renal epithelia
• Prolonged immobilisation
• Increased uric acid levels I.e taking increased purine subs – promotes crystalisation of Ca and oxalate
• ?? Nanobacteria – seen in 97% of renal stones
Types of stones composition

1. Calcium stones account for 80% of all kidney stones
   - Calcium oxalate (monohydrate and dihydrate) the most common
   - Calcium phosphate
2. Uric acid stones
3. Struvite stones (composed of magnesium, ammonium, calcium and phosphate)
4. Cystine stones
5. Drug-associated stones (Vit.D, Indinavir, ceftriaxon etc.)
6. Xantine stones (very rare)
# Underlying diseases and conditions for nephrolithiasis

<table>
<thead>
<tr>
<th>Stones composition</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium oxalate</strong></td>
<td>$\uparrow$ Ca, $\uparrow$ Ox, $\downarrow$ Cit, $\uparrow$ UA (idiopathic hypercalciuria, PHO, secondary HO)</td>
</tr>
<tr>
<td><strong>Struvit</strong></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td><strong>Calcium phosphate</strong></td>
<td>Urinary tract infection, distal RTA, immobilization, $\uparrow$ PTH</td>
</tr>
<tr>
<td><strong>Uric acid</strong></td>
<td>Hyperuricosuria, $\downarrow$ urine pH</td>
</tr>
<tr>
<td><strong>Ammonium urate</strong></td>
<td>Urinary tract infection, endemic</td>
</tr>
<tr>
<td><strong>Cystine</strong></td>
<td>Cystinuria</td>
</tr>
</tbody>
</table>

*Leumann & Hoppe, 1997, adapted*
120 детей с 11.2008 по 07.2015
окс 74,
вев 19,
вед 34,
в+в 21
фосф 18
струвит 3
моч к-та 9,
дигидрат 3,
тригидроксипурин 4,
урат аммония 2
цистин 6
окс+фосф 6
окс+моч 4

62% (74) оксалат кальция (вевелит 16%, веделит 28%, вев+вед 18%)
15% (18) фосфат кальция
8% (9) из моч к-ты (дигидрат моч к-ты 3%, тригидроксипурин 3%, урат аммония 2%)
3% (3) струвит
5% (6) L-цистин
8% (10) смешанные (окс+фосф 5%, окс+моч 3%)
Clinical presentation

- Often asymptomatic or symptoms of concomitant disease
- Renal colic/pain
- Urinary tract infection
- Dysuria
- Hematuria (up to 30% - gross hematuria)
Investigation-1

• Visualization
  – US informative in most cases except of urethral stones localization
  – Non-contrast CT for that and other cases
  – Intravenous pyelography to evaluate obstruction
Investigation-2

- **Urine tests**
  - Ca, Na, K, Cl, P, uric acid, pH, bicarbonate, creatinin, oxalate, citrate, culture, albumin, sediment

- **Blood tests**
  - Ca, Na, K, Cl, uric acid, pH, bicarbonate, creatinin, PTH, vit.D, molecular genetic

Table 4. Normal Urinary Values in School-age Children Based on 24-hour Urine Collection

<table>
<thead>
<tr>
<th>Calcium</th>
<th>&lt;4 mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate</td>
<td>&lt;50 mg/1.73 m² per day</td>
</tr>
<tr>
<td>Cystine</td>
<td>&lt;60 mg/1.73 m² per day</td>
</tr>
<tr>
<td>Citrate</td>
<td>&gt;400 mg/g creatinine</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&lt;0.56 mg/dL glomerular filtration rate</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt;20 mL/kg per day</td>
</tr>
</tbody>
</table>

Guidelines for Urolithiasis. www.uroweb.org/guidelines
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Crystals in urine

Ca oxalate monohydrate

Ca oxalate dihydrate

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Crystals in urine

Ca phosphate bruscite

Uric acid

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Crystals in urine

- Struvite
- Cystine

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Stones image

Cystine

Struvite staghorn

Calcium

Ca oxalate

Uric acid

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Stones analysis

• X-ray diffraction
• Infra-red spectroscopy
6 years old male

- Healthy parents, older sister with nephrocalcinosis, three healthy sibs
- Thirst and polyuria from infancy
- US-signs of nephrocalcinosis at 2 y.o.
- Urinalysis – WBC 10-20/hpf, no bacteria, pH 5.0-6.0
- Urinary oxalate >50 mg/24h, normal Ca and P
- Blood pH 7.427
- Serum creatinin 80 µmol/l (GFR 67.2 ml/min)
- Renal colic and stone passage at 5 y.o.
- Stone composition (X-ray diffraction): Calcium oxalate monohydrat (Whevellite)
- AGXT gene sequencing: HI971435(c.33dupC) + deletion c.959_960delCA).
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Family with PHO-I

1 ex. c.33 dup C

10 ex. c.959-960 del CA

18
13
12
10
6

1 ex. c.33 dup C
1 ex. c.33 dup C
1 ex. c.33 dup C
1 ex. c.33 dup C

10 ex. c.959-960 del CA
10 ex. c.959-960 del CA
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10 ex. c.959-960 del CA

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Primary hyperoxaluria

- **Type I**: Alanin-glyoxilate aminotransferase (AGT) deficiency in the liver due to mutations in AGXT gene. Urinary oxalate and glycolate increased.

- **Type II**: Glyoxilate reductase deficiency with L-glycerate hyperexcretion (better prognosis)

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Treatment of primary hyperoxaluria

- High fluid intake (>2 l/ m²)
- Citrate K/Na (100-150 mg/kg/day)
- Hydroxychlorothiazide (?)
- Piridoxin (Vit B6) 5-10 mg/kg/day
- ESWL
- Combined liver and preemptive kidney Tx

_Cochat et al, 2014_
Severe oxalosis (C.346G>A u C.508G>A AGXT)
Absorptive hyperoxaluria

- In Crohn disease and short bowel syndrome
- Normal people absorb < 5% of dietary oxalate
- Foods rich in oxalate (spinach, chocolate, beets, peanuts) can ↑ absorption 25 - 50%
- Low calcium diets ↑ intestinal absorption and urinary oxalate excretion
Cystinuria

• Autosomal recessive disorder caused by a tubular defect in dibasic amino acid transport
• Excrete excessive amounts of cystine, ornithine, lysine and arginine
• Cystine is soluble in the urine to a level of only 24 - 48 mg/dl
• In affected patients, the excretion is 480 - 3500 mg/day
• Stones of medium radio opacity
Cystinuria

• Treatment
  – increase urine volume to maintain solubility (240 - 480 mg/l)
  – urine pH > 7.5 (K citrate)
  – Restrict dietary sodium
  – Tiopronin or D-penicillamine bind cystine and reduce urine supersaturation
  – Surgery difficult
  – High recurrence
  – Rarely progress to ESRD

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Uric acid stones

- Urinary pH < 5.5, ↓ urine volume
  Hyperuricosuria
  - Genetic overproduction (Leich-Nyhan syndrome etc.)
  - Myeloproliferative disorders
  - High purine diet
  - Drugs
- Radiolucent
- Treatment: ↑ fluid intake, ↓ purine diet, urinary alkalinization (pH 6.5 - 7.0) with potassium citrate, allopurinol to reduce 24 hour uric acid excretion

_Ngo & Assimos, 2007
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Struvite stones

- Magnesium ammonium phosphate
- More common in women than men
- Most common cause of staghorn calculi
- Grow rapidly, may lead to severe pyelonephritis or urosepsis, obstruction and renal failure
- Heterogenous and laminated on X-ray
- Caused often by infections by organisms with urease (Proteus, Klebsiella, Pseudomonas, and Serratia)
- Hydrolysis of urea yields ammonia and hydroxyl ions, consumes H+ and thus ▲ urine pH
- ▲ urine pH increases saturation of struvite
- Treatment: Complete removal, prolonged antibiotic course, fluid, avoid alkali

K.Bichler, 2002
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Treatment of colic

- Fluid if obstruction is not severe
- Pain: NSAID or morphine
- Prednisolone
- Nifedipine
Stone removal procedures

- Stones <5 mm pass spontaneously
- ESWL
- Percutaneous nephrolithotomy (PNL)
- Open surgery
- Ureteroscopy
Urolithiasis. General considerations.

- Give more water
- Restrict sodium, protein and fat
- Treat UTI
- Do not restrict calcium
- Adjust urine pH according to stone composition/ethiology
- ESWL when stones>1 cm. Try to remove stones completely
- Metaphylaxis usually life long

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Nephrocalcinosis

- May be a consequence of furosemid and corticosteroid treatment in premature babies
- Usually does not progress in that cases
- Most of other causes are genetic
Williams syndrome

- 1:7500-20000
- Microdeletions in elastin gene
- “Elphin” facies
- Aortal stenosis, other cardiac abnormalities
- Muscular hypotony, motoric delay
- Hypercalcemia, Calciuria, nephrocalcinosis

- 6 months female: 6,7 kg, 70 cm
  - Ca – до 2,88 mmol/l, Ca$_2^+$ 1,41 mmol/l
  - P – 1,78 mmol/l
  - Creatinin – 49 mcmol/l
  - PTH – 14.80 pg/ml
  - pH 7.398, SB 25.6 mmol/l

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Distal Renal Tubular acidosis

- Most of patients with Type I RTA have nephrocalcinosis or nephrolithiasis (Ca phosphate) or both
- Mechanism for stone formation
  - Hypocitraturia due to acidosis
  - Hypercalciuria: acidosis ↑ bone resorption
  - Alkaline urine pH: defect in H+ excretion
- Rickets, poor growth
- Treatment: water, K Citrate, thiazides if severe calciuria
Familial hypercalciuria with hypomagnesemia and nephrocalcinosis (FHHN)

- Rare autosomal-recessive disease
- Deficit of tight junction protein in thin ascendent part of Henle loop **Claudin 16 (**CLDN 16 gene**)**
- Defect of Ca and Mg reabsorbtion
- Manifestation: muscular hypotony, nephrocalcinosis, urolithiasis, polyuria, high PTH
- Can progress to CRD
- Treatment: citrate, thiazides, Mg

*M.Praga, 1995*

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Dent’s disease

- X-linked (proximal) tubular disorder (*CLCN5* gene)
- Fanconi syndrome (may be incomplete)
- Rickets ±
- Calciuria with low molecular weight proteinuria
- Nephrocalcinosis in most of affected
- May progress to ESRD
- Treatment: K citrate, hydrochlorothiazide (potassium control!!!), indomethacin (?)

H.K.Burgess, 2001
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Neonatal Bartter syndrome

• Hypokalemic hypochloremic metabolic alkalosis with polyuria and nephrocalcinosis (*ROMK2, NKCC2 genes*)
• Failure to thrive, poor survival
• Water, sodium and potassium replacement, indomethacin

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