Kidney Stone disease in children

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Definitions

- **Urolithiasis** - stones formed in the kidney but localized anywhere in the urinary tract (inc. primary bladder stones)

- **Nephrocalcinosis** - deposits of calcium salts in the tubules, tubular epithelium and/or interstitial tissue of the kidney (limitation: ultrasonographic finding)

- Often times they may appear together

- Occasionally, it is difficult to distinguish between them
Epidemiology

• The exact incidence - unknown
  – 10% of that in adults
  – 1:5500 - 1:1750 hospital admissions between 1999 and 2008

• The incidence of pediatric kidney stone disease steadily increases
  – Environmental factors (dietary habits, obesity/metabolic syndrome)
  – Increased awareness
Why is it important to study kidney stone formation?

- Morbidity
- Potential deterioration in kidney function
- A key to diagnose a metabolic disorder (sporadic or inherited)
- May lead to the diagnosis of a structural defect in the kidney and urinary tract
- Prevention
Clinical presentation

• Asymptomatic - especially if kidney stones
• Pain - abdominal or flank more likely with ureteral stones (>5yrs)
• Recurrent abdominal pain
• Gross hematuria (30-55%)
• Dysuria and urgency (if in bladder or urethra)
• UTI
History

• Previous kidney stone
• Family history of nephrolithiasis
• History of underlying renal or urinary tract abnormality
• History of underlying metabolic condition associated with nephrolithiasis
• Medications (indinavir, sulfadiazine)
• Recurrent UTI (urease-producing organisms)
Physical examination

- Abdominal exam for tenderness or mass
- Growth measurements - chronic condition such as RTA or Dent’s
- Temperature as presenting sign of UTI
- Hypertension and edema are suggestive of other renal conditions
Initial laboratory evaluation

• Urinalysis - watch for crystals

• Urine culture - exclude UTI
Cystine crystals

Urine sediment showing hexagonal cystine crystals that are essentially pathognomonic of cystinuria.

Courtesy of Harvard Medical School.
Diagnosis

• Ultrasonography
  – effective modality without radiation
  – Good for radiolucent stones
  – Limited in its ability to uncover small stones

• Non-contrast helical CT
  – The most sensitive modality for stones of all sizes in the kidneys and ureters
  – Radiation exposure should be adjusted to the weight and height of the patient
Calculus obstructing left ureter. CT scan shows a calculus in the proximal left ureter causing delayed excretion of contrast material from the left kidney (long arrow). All the contrast has been excreted from the normal functioning right kidney and is in the nondilated right ureter (small arrow). Courtesy of Jonathan Kruskal, MD.
**Staghorn calculus** CT scan without contrast shows large staghorn calculus in the right kidney (arrow).

Courtesy of Mark D Aronson, MD.
Abdominal plain radiography
- Detects radiopaque stones
- May miss radiolucent stones
- May miss small stones
- May miss stones that overlay bony structure
- May miss urinary obstruction
Staghorn calculus
The Stone is Not the Disease Itself; It is Only One Serious Sign

Hoppe B, Pediatr Nephrol 2010:25:403
Etiology

- Children are likely to have an underlying metabolic disorder
- A urinary metabolic risk profile may be found in up to 76% of children
- Higher rate of stone recurrence [30-65%] or progression of NC
- Prevention is imperative
- Genetic and anatomic causes are still the main determinants
There are different types of stones
Do not throw them away! Send them for analysis...
Recommended work-up for every child with a kidney stone

- Stone analysis may direct the metabolic evaluation
- Evaluation while the patient is at home, free of infection and consuming regular diet
- **Blood tests:** venous blood gases, electrolytes, calcium, phosphate, magnesium, uric acid, BUN/creatinine
Urine tests - preferably timed-urine collection:
- Urinalysis (inc. microscopy and metered pH)
- Volume, sodium, calcium, phosphate, magnesium, uric acid, protein, creatinine
- Oxalate, citrate (if hyperoxaluria – organic acid profile)
- Amino acid profile

In infants a urine sample can be used

Dietary evaluation ($H_2O$ intake, Na, Ca)
Normal urinary values based on 24h urine collection

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>&lt;4 mg/kg/day</td>
</tr>
<tr>
<td>Oxalate</td>
<td>&lt;50 mg/1.73m$^2$/day</td>
</tr>
<tr>
<td>Uric acid</td>
<td>&lt;815 mg/1.73m$^2$/day</td>
</tr>
<tr>
<td></td>
<td>&lt;18 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>&lt;0.56 mg/dl GFR</td>
</tr>
<tr>
<td>Citrate</td>
<td>&gt;400 mg/g creatinine</td>
</tr>
<tr>
<td>Cystine</td>
<td>&lt;60 mg/1.73m$^2$/day</td>
</tr>
<tr>
<td>Total volume</td>
<td>&gt;20 ml/kg/day</td>
</tr>
</tbody>
</table>
Single random urine sample

- **Calcium/creatinine**
  - Infants: <0.6 mg/mg
  - Children: <0.21 mg/mg

- **Oxalate/creatinine**
  - Infants <6mts: <0.3 mg/mg
  - Children <4yrs: <0.15 mg/mg
  - Children >4 yrs: <0.1 mg/mg

- **Uric acid**
  - <0.56mg/dl GFR

- **Citrate/creatinine**
  - >0.51 g/g
Diagnosis

• A 24-h urine collection for lithogenic and stone inhibitory parameters
• Spot urine in infants
• **Biochemical analysis of stone**
• **Genetic and/or biochemical testing for definite diagnosis**
Frequency of specific metabolic findings

- Hypercalciuria - 50%
- Hyperoxaluria - 10-20%
- Hyperuricosuria - 2-8%
- Cystinuria - 5%
- Hypocitraturia - 10%
Genetic diseases with kidney stones and/or nephrocalcinosis

- Classified according to their underlying metabolic derangement:
  - **Hypercalciuria** (± hypercalcemia)
    - Bartter syndrome
    - Dent’s disease
    - Familial hypomagnesemia with hypercalciuria and NC
    - Tyrosinemia type I
    - Liddle’s syndrome
    - Gordon’s syndrome
  - **Hyperoxaluria** (primary/secondary)
  - **Cystinuria**
  - **Hyper/hypouricosuria**
  - **RTA** (hypocitraturia and hypercalciuria)
Mechanisms of hypercalciuria

• Intestinal absorptive hypercalciuria
• Imbalance between bone formation and bone resorption
• Urinary calcium leak
• There is interaction between these mechanisms
Secondary renal hypercalciuria

- High salt diet
- Ketogenic diet
- Loop diuretics (furosemide)
- Steroids
- Immobilization
- High dose calcium or vitamin D
- Hypophosphatemia-induced increased 1,25(OH)_{2}D synthesis
Nephrocalcinosis in infants

- Precocious babies - compromised tubular function
- The use of steroids or furosemide
- Total parenteral nutrition
- Family history of kidney stones
- Hypercalciuria (occasionally hyperoxaluria)
- Complete resolution in 50%
Fluid intake

- Infants > 750 ml
- Toddlers (1-5 yrs) > 1000 ml
- Children (5-10 yrs) > 1500 ml
- Children (> 10 yrs) > 2000 ml
Management of hypercalciuria

- Increased water intake
- Low-salt diet
- Dietary calcium is not restricted (use RDA)
- If dietary measures fail - try thiazide diuretics

- If everything else fails:
  - K-citrate
  - Phosphate supplement
Primary hyperoxalurias

- Rare autosomal recessive disorders of endogenous oxalate synthesis

- Calcium salt of oxalate is insoluble

- Hyperoxaluria results in renal stone formation, nephrocalcinosis, kidney failure and multi-system disease
The hyperoxalurias

- **PHI** - absent, deficient or mistargeted activity of alanine-glyoxylate aminotransferase (AGT)

- **PHII** - deficiency of glyoxylate reductase/hydroxypyruvate reductase (GRHPR)

- **PHIII** - deficiency of mitochondrial 4-hydroxy 2-oxoglutarate aldolase
1 - hydroxyproline oxidase
2 - PC dehydrogenase
3 – Asp-amino-transferase
4 – HOGA1
5 - GRHPR
6 - GO
7 - AGT1

COLLAGEN TURNOVER; MEAT CONSUMPTION

OXALATE

MITOCHONDRION

pyrroline-hydroxy-carboxylate → hydroxy-glutamate

HOG

pyruvate

GLYOXYLATE

GLYCINE

AGT

PEROXISOME

GLYOXYLATE

GLYCOLATE

GRHPR

OXALATE

LDH

HYDROXYPROLINE
Management of hyperoxaluria

• Increased water intake
• Pyridoxine for patients with PH1
• Citrate (intestinal calcium binding and alkanization of urine)
• Avoid excess vitamin C
• Avoid low-calcium diet (enhances oxalate absorption)
• Magnesium or pyrophosphate supplementation (inhibit calcium-oxalate precipitation)
Management of hyperuricosuria

• High fluid intake
• Needs to address constituents of the metabolic syndrome
• Low purine diet
• Alkalinization of urine
• Allopurinol
Of UTI’s and kidney stones

• Struvite stones are produced by urease-expressing bacteria like Proteus

• The hydrolysis of urea produces ammonium and bicarbonate

• Super-saturation of ammonium, Mg and P, in an alkaline urine, results in stone formation

• Otherwise, UTI is secondary to an obstructing kidney stone
Acute management of kidney stones

- Fluid intake (enteral or intavenous)
- Pain control (NSAID or opiate therapy)
- Treat UTI if present
- Most stones < 5 mm in diameter will pass spontaneously with increased urine flow
- Alpha blockers may be used to facilitate passage of distal ureteral stones
- Stone retrieval - the child/family should be instructed to strain the urine
Urologic intervention

• Indications
  – Unremitting severe pain (usually associated with obstruction)
  – Obstruction with compromised renal function

• Procedures
  – Extracorporeal shock wave lithotripsy (ESWL)
  – Percutaneous nephrolithotomy (PCNL)
  – Ureteroscopy
Follow-up

- High rate of recurrence
- High recurrence among children with underlying metabolic disorder
- Compliance is imperative
- Regular follow-up of the metabolic derangement and urine output
- Periodic ultrasound (stone enlargement, new stones and/or hydronephrosis
- Periodic assessment of kidney function
Thank you!

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