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Urolithiasis in Children—Treatment and Prevention

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Opinion statement

The incidence of stones is increasing in children especially among Caucasian adolescents. Every child with stones deserves an evaluation because the majority has a diagnosable metabolic defect and 50 % will have a recurrence of stones. Diet, sedentary lifestyle, and climate change contribute to the changing frequency of stones. There is some evidence to support the following lifestyle changes: high fluid intake, low sugar intake, low sodium intake, higher plant protein intake and lower animal protein intake, normal calcium intake, high potassium citrate intake, moderate exercise, and reduced environmental temperature. Our challenge is to help our patients commit to and maintain a healthy lifestyle. After dietary influences, having a family member with nephrolithiasis poses the greatest risk. Identifying the underlying defect that permits stones to form in some members of the family will permit targeted therapy. For instance there is a "gain of function" mutation in the calcium-sensing receptor gene in families with autosomal dominant hypocalcemic hypercalciuria. Treating these patients with vitamin D to increase the blood calcium results in marked hypercalciuria, nephrocalcinosis, and nephrolithiasis. Thus, the second challenge in addition to lifestyle changes is to identify the gene defects permitting stone formation.

Introduction

The type of urolithiasis in children has been changing in the past three decades from infectious to metabolic with hypercalciuria and hypocitraturia being the most common metabolic derangements. The incidence of stones in both adults and children has increased over the last decade with one single center experience showing a fivefold increase [1]. Over the past decade, our own center has shown stable numbers of stones in children

age 0–3 and 4–8 years but a doubling of stones presenting to the clinic or emergency room in the age range 9–13 and 14–18 years (Fig. 1).

The incidence of stones in African American children remains low and unchanged. The increase is primarily among Caucasians. Since the genetic predisposition to stones is likely not changing, the increased incidence is felt to be lifestyle, nutrition, and climate change. Seventy percent of children will have a diagnosable metabolic derangement [2], and more than 50 % of those treated surgically will have a recurrence of stones so evaluation is appropriate at the time of the first stone [3••].

Few stones can be dissolved once formed. Uric acid stones may be dissolved with alkali therapy, small cystine stones may resolve with thiols, alkalinization, and high fluid. Therefore, medical management of stones consists primarily of prevention of new stones. Determining the underlying metabolic disorder guides preventive therapy. A 24-h urine for metabolic stone profile, stone analysis if available, and blood testing that generally includes kidney function, electrolytes, calcium, and phosphorus are the basic tests but can be expanded as dictated by the 24-h urine testing. Genetic determinants of hypercalciuria are categorized based on PTH and serum calcium [4] (Table 1). Rare causes of kidney stones that may eventually impair renal function may be suspected based on certain clinical features and urinalysis.

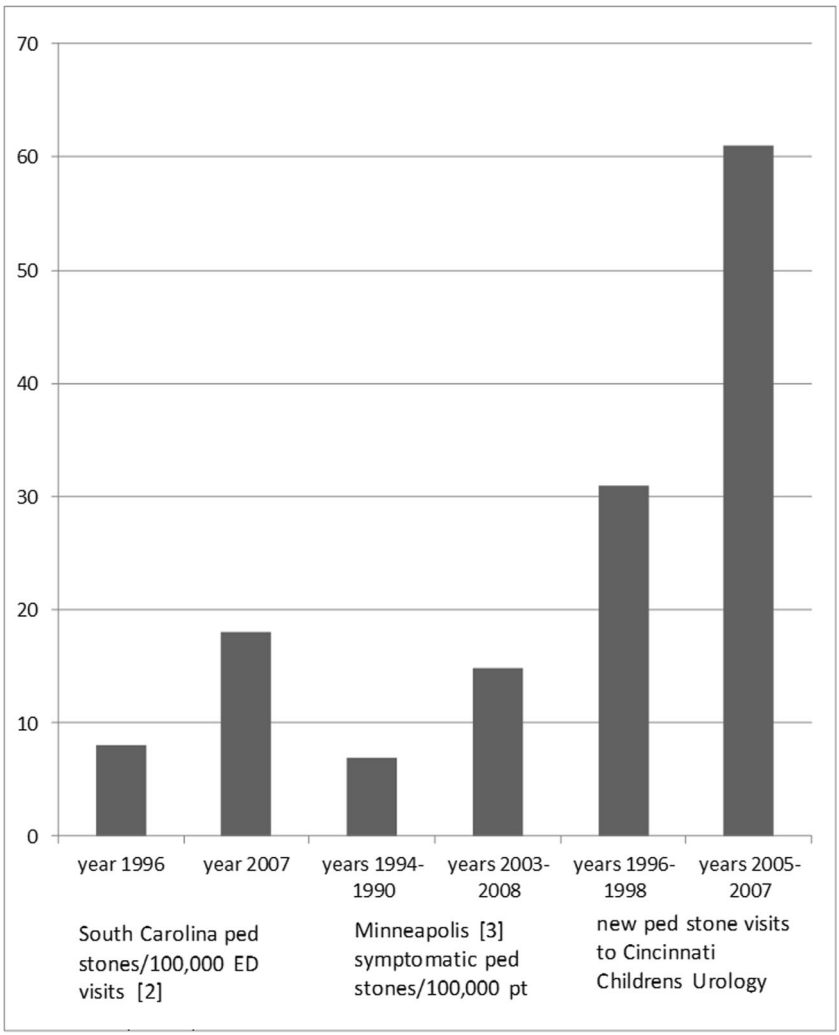

Fig. 1. Sampling of the increasing incidence of stones in pediatric patients across the country.

Table 1. Unusual features of kidney stones in children that may suggest a more serious and chronic kidney disorder

Clinical history	Urinalysis	Imaging
Onset of stones in childhood, family history of stones or nephrocalcinosis or unexplained renal failure, reddish-brown diaper stain, growth retardation or rickets	Cystine crystals, unidentified crystals, 2,8-dihydroxyadenine crystals, proteinuria	Nephrocalcinosis, radiolucent kidney stones, multiple stones, bilateral stones

Adapted from hereditary causes of kidney stones and chronic kidney disease [36••]

In the diagnosis of stones, computerized tomography (CT scan) without contrast can identify stones and is readily available, but the radiation dose is cumulative in children who may have many episodes of stones in their lifetime. The preferred modality for evaluating stones in children is the renal ultrasound which can identify most significant stones and underlying anatomic abnormalities [5, 6].

Treatment

Diet and lifestyle

- While adults are recommended to stay well hydrated to produce a goal of 2.5 l of urine daily, children should drink enough to produce 35 ml of urine per kg daily [5]. More urine output decreases the super saturation of calcium oxalate, calcium phosphate, and uric acid [7].
- Children should be provided a note for school to allow water bottles and more frequent bathroom breaks.
- The likelihood of preventing nephrolithiasis is dependent on the type of fluid. Consumption of sugary drinks such as soda-pop or fruit juice sweetened with high-fructose corn syrup has been associated with increased risk of incident kidney stones [8]. Lemonade consumption has been shown to reduce recurrence in adults with hypocitraturic nephrolithiasis in some studies [9] but not in others [10, 11•]. The accompanying cation is important. If the content of the food or fluid is primarily citric acid, the citrate is neutralized and does not increase the urinary citrate. With foods and fluids high in potassium citrate (orange juice, some powdered lemonade mixes) and not citric acid, urinary citrate can increase. Calorie intake needs to be considered with these beverages as well.
- Sodium intake should be limited to less than 2–3 mEq/kg/day for young children or less than 2.4 g in adolescents or adults [12••]. 2300 mg sodium is contained in 1 level teaspoon of salt. Sodium and calcium compete for passive reabsorption along the nephron; an increase in sodium intake will directly increase calciuria. The amount of sodium in the urine reflects the sodium in the diet if the child is in a normal state of hydration and if no diuretics are being used.

- Calcium intake should not be limited. In fact, low calcium diets have been associated with increased risk of nephrolithiasis while high dietary calcium intake has been associated with decreased risk of stones in adults [13]. This is likely due to the ability of dietary calcium to decrease the intestinal absorption of oxalate.
- Obesity has been associated with stone risk in adults before and after surgery. A recent study in obese adolescents found similar calcium, uric acid, citrate before and after surgery but oxalate excretion increased significantly after roux en Y gastric bypass compared with the group who had a sleeve gastrectomy [14].
- Borghi et al. found a reduction in recurrence of calcium oxalate stones when comparing a normal calcium, low-animal-protein, low-sodium diet to a traditional low-calcium diet [15], Class I. The benefit offered by low-animal-protein is believed to be by reducing the intake of purines. Purines increase urinary uric acid. Diets high in protein can also increase the fixed acid load leading to hypercalciuria by an increase in bone reabsorption. Furthermore, high amounts of animal protein may lead to hyperoxaluria by increase in oxalate intestinal absorption along with stimulation of endogenous oxalate production [7]. During the growing years, children should not be protein restricted but excessive protein intake may be curtailed.

Pharmacologic treatment

- Drug: tamsulosin

Goal of treatment:	Assist in passage of ureteral stones known as medical expulsive therapy (MET). The data suggests that there is a higher spontaneous passage rate with tamsulosin in children as there is in adults. Tamsulosin is usually prescribed only during stone passage. The adjusted odds of stone passage were 3.31 times higher in children prescribed with tamsulosin. [12••] An abstract suggests that tamsulosin did not improve the passage of stone fragments after ESWL for large pelvic stones [16].
Class of drug:	Alpha blocker
Dosage:	Dosage was not widely reported, but in one study, a dose of 0.01 mg/kg was used to a max of 0.4 mg which is the size of the capsule.
In other studies:	2 to 4 years: Oral, 0.2 or 0.4 mg once daily at bedtime
Children >4 years and adolescents:	Oral, 0.4 mg once daily at bedtime
Contraindications:	Hypersensitivity to tamsulosin
Main drug interactions:	Antihypertensives may enhance the hypotensive effects of tamsulosin.
Main side effects:	In the 465 children treated with tamsulosin for stone disease, there was only one withdrawal. Main concerns are orthostatic hypotension so the dose is usually started right at bedtime. Intraoperative floppy iris syndrome has been noted in adults and can complicate cataract surgery. Priapism has been reported. Sulfonamide allergy—rarely, there can be a reaction to tamsulosin among patients with severe sulfonamide allergy. Use with caution if there is a sulfonamide allergy.

Special points: In a retrospective study of pregnant women receiving tamsulosin for stone therapy, there did not seem to be a deleterious effect on the fetus or the mother [17]. The manufacturer recommends not opening the capsule, but in the studies, the capsules were opened and sprinkled on food as needed.

- Drug: Potassium citrate

Goal of treatment: Stone prevention in calcium or cystine stones disease, dissolution and prevention of uric acid stones, and treatment of metabolic acidosis leading to stone disease

Dose: Infants and children, 2–3 meq bicarbonate-equivalent/kg/day divided into 3–4 doses. Dose should be adjusted according to the amount of calcium in the urine and the alkalinity of the urine. Adults, 30–60 meq bicarbonate-equivalent/dose at meals and bedtime.

Contraindications: Severe renal insufficiency, oliguria, or azotemia; potassium-restricted diet; untreated Addison's disease; adynamia episodica hereditaria; acute dehydration; heat cramps; anuria; severe myocardial damage; and hyperkalemia from any cause. While not necessarily contraindicated, severe hepatic dysfunction may impair the conversion of citrate to bicarbonate.

Drug interactions: ACE inhibitors and ARBs may increase risk of hyperkalemia, potassium sparing diuretics may increase the risk of hyperkalemia, heparin and low molecular weight heparin may enhance the effect of potassium salts. In aluminum hydroxide, citric acid derivatives may enhance the absorption of aluminum.

Main side effects: Gastrointestinal: stomach pain, nausea, vomiting, diarrhea, may cause bleeding, ulceration, perforation or obstruction, and hyperkalemia

Special points: In one study, the urinary calcium to citrate ratio was helpful in determining which hypercalciuric patients were likely to develop stones [18].
One study noted improved bone density in children with hypercalciuria who were treated with potassium citrate rather than attempts to improve bone density with dietary measures alone [19].
The ketogenic diet, which is an acid load, depletes citrate and increases urinary calcium. Beginning potassium citrate at the time of the institution of the ketogenic diet reduced the incidence of stones [20].
The risk of calcium phosphate stones increases above a urine pH of 7.

- Drug: thiazides:

Goal of treatment: Reduction of urinary calcium by increasing calcium reabsorption in the tubules

Dose: Hydrochlorothiazide 1–2 mg/kg/day in a single dose adjusted by the urinary calcium, max dose 100 mg; half-life, 5.6–14.8 h.
Chlorthalidone initial: 0.3 mg/kg once daily; may titrate up to a maximum daily dose of 2 mg/kg/day or 50 mg/day; half-life, 40–60 h.
Chlorothiazide 10–20 mg/kg/day in divided doses once or twice daily; half-life, 45–120 min.

Contraindications: Hypersensitivity to hydrochlorothiazide, any component of the formulation, sulfonamide-derived drugs, and anuria

Drug interactions: Antihypertensives (including alpha blockers that might be used to help with stone passage) increased hypotensive effect.

Drugs with hypokalemic effects such as corticosteroids:	increased risk of hypokalemia.
Antidiabetic drugs:	diminished effect of antidiabetic agents with concurrent use of thiazides.
Carbamazepine:	increased risk of hyponatremia.
Lithium:	increased risk of lithium toxicity.
Selective serotonin reuptake inhibitors:	may enhance the hyponatremic effect of thiazide diuretics.
Thiazide diuretics:	may enhance the hypokalemic effect of topiramate and may increase the serum concentration of topiramate.
Main side effects:	Hypotension, dizziness, headache, skin photosensitivity, glycosuria, hyperglycemia, hyperuricemia, abdominal cramps, anorexia, impotence, anemia, jaundice, muscle spasm, weakness, interstitial nephritis. Rare but important or life-threatening are allergic myocarditis, eosinophilic pneumonitis, hepatic insufficiency, lip cancer, and systemic lupus erythematosus.
Special points:	Among adult hypertension clinics, there is still a debate about the risk of long-term thiazides which clearly decrease blood pressure and risk of stroke but may not reduce the risk of myocardial infarction due to possible changes in glucose, insulin, and cholesterol [21]. In children, the goal is to use thiazides to reduce hypercalciuria for a year or less, if possible, in order to change other stone risk factors. Strong consideration should be made of beginning potassium citrate in the hypocitraturic patient as this may be accentuated due to the hypokalemia induced by thiazides and lead to recurrent stones. Addition of potassium as chloride if the urine is already alkaline or citrate if the urine pH is not high may be beneficial when thiazides are started even if the patient does not have hypocitraturia because thiazide-induced hypokalemia will deplete urinary citrate and decrease the benefit of thiazides in preventing stones.

- Drug: allopurinol

Goal of treatment:	Reduce high urinary uric acid levels that can be the underlying cause of recurrent calcium oxalate stones.
Category of drug:	Uric acid-lowering agent, xanthine oxidase inhibitor
Standard dosage:	Recurrent calcium oxalate renal stones. Children and adolescents, 4 to 10 mg/kg/day in divided doses 3 to 4 times daily; maximum daily dose, 300 mg/day [22••].
Contraindications:	Hypersensitivity to allopurinol or components of formulation
Main drug interactions:	Therapy modification as the risks outweigh the benefits is considered: ACE inhibitors, azathioprine, mercaptopurine, antacids, vitamin K antagonists like warfarin and others. Interaction possible. Weigh benefits and risks when using with the following drugs: amoxicillin, carbamazepine, loop diuretics, thiazides, theophylline, and others.
Main side effects:	Skin rash, acute gout (especially when starting), diarrhea, nausea, increase liver enzymes. Rare or life threatening: ageusia, alopecia, Stevens-Johnson syndrome, hepatotoxicity, nephritis, and others.
Special points:	Oversuppression of uric acid production may lead to xanthine stones which are much harder to dissolve than uric acid stones. If supersaturation of uric acid in the urine is high (usually with an acid urine), increasing solubility with citrate and volume can be beneficial without

allopurinol. Lowering dietary purine load can be helpful (but difficult) unless the high uric acid is due to a metabolic syndrome or tumor lysis.

- Drug: tiopronin [23]

Goal of treatment:	Bind cystine to bring the total cystine below the solubility limit of 250 mg/l
Category of drug:	Reducing agent that exchanges with one cysteine in the cystine molecule to form a more soluble tiopronin-cystine disulfide
Dose:	1 g of tiopronin binds 250 mg of cystine approximately so if the total cystine excretion is 750 mg/day, urine output can be increased to over 3 l or urine output can be increased to 2 l and 1 g of tiopronin added in divided doses at least three times a day as the excretion is rapid and once or twice a day dosing is not protective. In general, adults are started at about 800 mg/day and children at 15 mg/kg/day (though not FDA approved below age 9) with adjustments based on cystine levels. However, urine assays may be measuring both cystine and cystine-tiopronin complexes. Some companies which perform urinary stone risk assays have the ability to assess free cystine.
Contraindications:	History of myelosuppression while on tiopronin, pregnancy, and lactation
Main drug interactions:	None found
Main side effects:	Disorders of the skin, oral ulcers, GI symptoms, taste alterations, hypersensitivity reactions, sense of smell altered, aplastic anemia, leukopenia, thrombocytopenia, kidney disease, drug fever, and drug-induced lupus
Special points:	Monitor cystine levels at 1 month then every 3 months, 24-h urinary protein, urinalysis, CBC, serum electrolytes, hepatic function every 3–6 months, and renal/bladder ultrasound yearly and with symptoms. In addition to tiopronin, high urine volume and alkalinization improves solubility of cystine. Care must be taken when urine is alkalinized as the supersaturation of calcium phosphate may increase leading to calcium phosphate not cystine stones. The supply of tiopronin has been unpredictable. The orphan drug company Retrophin is now the sole supplier of tiopronin in the USA and is the med hub for distribution to the patients.

- Drug: penicillamine [23]

Goal of therapy:	Make cystine more soluble in patients with cystinuria
Category:	Chelates heavy metals like iron, copper, zinc, and chelates cystine
Dose:	Children, 30 mg/kg/day in four divided doses; maximum dose, 4 g/day
Adults:	Initial, 2 g/day divided every 6 h (range, 1–4 g/day)
Contraindications:	Patients with previous aplastic anemia or agranulocytopenia with penicillamine, pregnancy, or lactation
Main drug interactions:	Antacids, oral iron salts, digoxin, multivitamin and minerals, polaprezinc, hematopoietic suppressive drugs
Main side effects:	Allergic reactions, bronchiolitis obliterans, skin friability, drug fever, taste alterations which usually disappear with continued use, Goodpasture's syndrome, hematologic abnormalities, hepatotoxicity, drug-induced lupus, pemphigus, proteinuria/hematuria, myasthenia gravis, and others.

Special points: Penicillamine interferes with the function of B6 and patients on penicillamine should be supplemented with additional B6 usually 25 mg daily for adults.

- Drug: calcium

Goal of therapy: Provide recommended daily dietary allowance and bind oxalate and phosphate to prevent absorption in the intestinal tract.

Category: Nutritional supplement

Recommended Dietary Allowance of Calcium

Dose:
0–6 months, 250
6–12 months, 260
1–3 years old, 700
4–8 years old, 1000
9–13 years old, 1300
14–18 years old, 1300
19–30 years old, 1000
31–50 years old, 1000
51–70 years old, 1000
51–70 year old, females, 1200
71+ years old, 1200
14–18 years old, pregnant/lactating, 1300
19–50 years old, pregnant/lactating, 1000

NIH: Institute of Medicine, December 2010

Contraindications: excessive calcium intake

Special points: Oxalate absorption increases with low calcium diet [42]. Stone rate did not decrease in adult stone forming men on a low-calcium diet [13]. Low-calcium diet can induce a negative calcium balance jeopardizing bone mineralization [24].

- Drug: bisphosphonates

Goal of therapy: Improve bone density, decrease fractures, and decrease hypercalciuria and stones

Category: Bisphosphonate which decreases osteoclastic bone resorption

Dose: Depends on the drug. There are IV forms for children who cannot sit or stand after administration orally.

Contraindications: Hypersensitivity, esophageal disorders, low serum calcium, and inability to stand or sit for 30 min after taking orally. Not recommended if creatinine clearance is <35 ml/min.

Main drug interactions: Antacids, calcium, magnesium, iron, multivitamins, proton-pump inhibitors may decrease the effect. Non-steroidals, aspirin, and aminoglycosides my increase the effect. All foods and beverages interfere with absorption.

Main side effects: Hypocalcemic, esophageal or gastric ulcer, abdominal pain, atypical femur fractures, bone-joint-muscle pain, osteonecrosis of the jaw, and difficulty with oral surgery such as dental implants.

Special points: Bisphosphonates have been used in children with hypercalciuria and low bone density [25], but new bone formation may not be normal and bisphosphonates remain in the bone for years. It is likely that the risks

outweigh the benefits unless there are fractures associated with the low bone density and stones.

Interventional procedures

Intervention for stones

1. Outpatient management of acute stone episode
a. Oral hydration
b. Analgesics usually narcotics
c. Consider alpha blockers
2. Indications for inpatient admission and/or acute surgical intervention
a. Solitary kidney with obstruction
b. Fever with signs of sepsis
c. Intractable nausea and/or vomiting
d. Poor pain control with analgesics
e. High-grade obstruction
f. Previous reconstruction of the urinary tract making spontaneous passage unlikely
3. Choice of surgery [26]

The goal is to render the child stone free in one treatment. The extent of stone disease and anatomic considerations will guide surgeon to determine what surgical modality is best suited for the patient. Residual fragments previously thought to be clinically insignificant led to symptomatic stones or enlargement of stones on follow-up. The risk of stone enlargement was greatly increased if the fragments were left in a child with an underlying metabolic risk factor [27, 28]. Therefore, stone free at conclusion of the procedure is optimal outcome rather than rely upon spontaneous passage in postoperative state.

4. Comparison of extracorporeal shock wave (ESWL) therapy and ureteroscopy in children (Table 2)
5. Percutaneous nephrolithotomy (PCNL)
Indications for PCNL are as follows:

Staghorn calculi
Stones >2 cm
Lower pole stones >1 cm
Cystine stones
Failure of other treatments
Associated anatomical anomalies (UPJ obstruction, calyceal diverticulum, horseshoe kidney)

Complications of PCNL (greatly reduced by the institution of the minipercutaneous nephrolithotomy or mini-perc using 11 F instruments compared with the standard adult equipment 24–34 F) are as follows:

Hemorrhage (in 4 pediatric studies with 287 patients only 1 required a blood transfusion.) [26]

Table 2. Risk and benefit of ESWL and ureteroscopy in the management of pediatric stone disease

ESWL	Ureterorenoscopy
Non-invasive	Minimally invasive
Stones must be visible on x-ray	Treated under direct visualization
Safe in young children	Scope may not fit in ureter
Lithotripter may not be readily available	Laser always available
Multiple stones may require second procedure	All visualized stones can be treated
Typically no stent mandatory if stone <1 cm	May requires stent depending upon extent of procedure
57–92 % success rate	86–100 % success rate (highest with ureteral stones)
No long-term renal damage [37] but more hypertension and diabetes in adults [38]	2/287 children developed ureteral strictures and 8/287 had low grade reflux [39]
Lower success if stone in lower calyces. Infundibulopelvic-ureteropelvic angle predicted the ability of stone fragments to pass after ESWL to stones in lower calyces [40, 41]	Same

Renal scarring/damage (none to minimal scarring on subsequent DMSA scans, 1 in 65 had worsening renal function on DMSA scan) [29]
Post-operative fever in 30 %
Damage to other organs (rare)
Fluid extravasation

Physical/speech therapy and exercise

Acute vigorous exercise increases calciuria [30]. Children and adults should be advised to hydrate well during strenuous exercise.

Regular, even modest, exercise was associated with a lower incidence of kidney stones in postmenopausal women [31]. Sedentary lifestyle may be partially responsible for the increase of stones in children and young adults and should be evaluated.

Dyslipidemia and the metabolic syndrome in children are associated with urinary citrate depletion due to a higher acid load. Higher urine uric acid and higher urine oxalate may also occur [32].

Surgery for obesity in adolescents is associated with higher urinary oxalate among those with Roux-en-Y bypass surgery compared with those who had gastric sleeve surgery [14].

Pediatric conclusions

There are a few management tips that I have found especially useful.

- Among children with low muscle mass (Duchenne muscular dystrophy, spina bifida, spinal cord injury, etc.), the urine calcium to osmolar ratio is more helpful than the calcium to creatinine ratio. Calcium mg/dl divided by osmolality mosm/l and multiplied by 10 should be less

than 0.25 [33]. The calcium in a 24-h urine is unaffected but judging the adequacy of collection based on the 24-h creatinine is inaccurate.
- Children on the ketogenic diet or modified Adkins diet for seizures have a higher incidence of stones due to an acid load that depletes citrate and releases calcium from the bone. Supplementing with potassium citrate when the ketogenic diet is started can decrease or eliminate stone risk [20].
- Topiramate (and zonisamide and acetazolamide) slightly increased the risk of stones in initial clinical studies, but among children with significant disabilities, the risk of stones may be much higher approaching 50 % in those treated with topiramate [34].
- Stones associated with an ileostomy are usually uric acid due to the concentrated acidic urine produced when the colon is not available to reabsorb water and bicarbonate.
- Among children with hypercalciuria, the citrate level affected whether or not the children were stone formers. A calcium/citrate ratio >0.326 helped to identify high-risk hypercalciuric children [18].
- Children with hypercalciuria may be at risk for low bone density [35]. A bone density should be checked if there is persistent hypercalciuria or bone fractures.

Compliance with ethical standards

Conflict of interest
Elizabeth C. Jackson declares that she has no conflict of interest. Mary Avendt-Reeber declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Paper of particular interest, published recently, have been highlighted as:
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