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Kidney Stones in children

1. Introduction
In the past decade, a significant increase in both incidence and prevalence of adult nephrolithiasis has been noted in industrialized countries. In pediatric patients, hospitalization for kidney stone disease has steadily increased. Definite incidence rates are, however, not available for nephrolithiasis in children. The increase of stone disease in adults is most likely related to changing environmental factors such as dietary habits, decreased fluid intake and obesity. While these factors clearly play a role in pediatric population, genetic, metabolic and anatomical causes are still the main determinants. Because of the 50% likelihood of finding an underlying metabolic cause for stone formation in younger children, a metabolic workup is recommended for all children with stone disease, including first-time stone formers.

2. Epidemiology
A large study incorporating a nationally representative sample suitable for defining the true incidence of nephrolithiasis in US children has not yet been done. Population-based data appropriate for defining incidence in pediatric patients are limited to studies done outside the United States and one study investigated state-wide data in South Carolina. In South Carolina, data from all pediatric emergency department visits the incidence of nephrolithiasis for children aged <18 years was found to be 18.5 per 100,000 children in 2007, an increase from 7.9 per 100,000 in 1996. On the basis of data from adult populations, nephrolithiasis affects men more than women. Pediatric nephrolithiasis, conversely, seems to be more common in girls on the basis of recent data. In the 2003 Kids Inpatient Database, the sex distribution among pediatric patients with stone formation varied significantly by age. In the first decade of age, a male predominance was found that had shifted to a female predominance in the second decade. In South Carolina, the male-to-female ratio is 1:1.4 for all children, and the discrepancy becomes more pronounced as children enter adolescence. Nephrolithiasis more commonly affects non-Hispanic white individuals as compared with non-Hispanic black individuals. This discrepancy seems to be true in the pediatric population as well. With regard to the Hispanic population, most studies (both adults and pediatric) have found that Hispanic individuals have a risk for nephrolithiasis that is higher than black individuals but not as high as for white individuals. The risk for kidney stones increases with age in adults up to a peak risk in the 50s and 60s, although some data reflect the highest risk for women to be in the late 20s and 30s. Extrapolation to pediatrics would predict lower risk with younger ages, and recent data support this. Sas DJ et al in their 12-year study from South Carolina, showed lowest incidence in children aged 0 to 3 years (0.6 per 100,000) and a consistent
increase through adolescence, when the overall incidence for children aged 14 to 18 years was 34.9 per 100,000. Children aged 14 to 18 years had a 10.2-times greater risk for nephrolithiasis compared with children aged 0 to 13 years. Older children are also more likely to have ureteral stones, whereas younger children more commonly have renal stones.

3. Pathophysiology
Renal stone formation progresses in successive steps. i) Nucleation: which is the phase change of dissolved salts into a solid. Nucleation can be either homogenous when crystal precipitation happens spontaneously in a supersaturated urine or heterogeneous when it occurs at lower degrees of saturation in the presence of nucleating agents (i.e. cells, crystals, urinary proteins or components of the epithelial cells). ii) Retention of the initial nucleus in sites of the urothelium; iii) Crystal’s growth; iv) Crystal’s aggregation.

There are three proposed pathogenic mechanisms of lithogenesis.

1. **The free particle theory:** Crystal precipitation is the result of homogenous nucleation of supersaturated urine in the tubular lumen of the distal nephron and necessitates high levels of ionic concentrations. The initial nucleus grows progressively in size and obstructs the collecting ducts. This is the presumed mechanism in the case of cystinuria and CaOx stones after gastric bypass surgery in obese patients. These patients present high urinary levels of cystine and oxalate, respectively, which favor intratubular homogenous nucleation. Histologically, there is no evidence of epithelial cell injury or interstitial fibrosis

2. **The fixed particle theory:** Intratubular crystals adhere to the tubular epithelium inducing cell injury and formation of nuclei. Fixed nuclei contact with supersaturated urine and crystals grow in size. These mechanisms induce intratubular nephrocalcinosis and may lead to nephrolithiasis and obstructive tubulopathy. Papillary biopsies in patients with brushite, cystine and apatite stones secondary to distal tubular acidosis revealed plugging of the inner medullary collecting ducts and
ducts of Bellini with apatite crystals, epithelial cell damage, inflammation and focal interstitial fibrosis. Protrusion of these mineral plugs in the lumen may initiate crystal growth.

3. **Interstitial apatite plaque (Randall’s plaque hypothesis):** In contrast to the above theories, it has been proven that calcium oxalate stones are formed upon an interstitial plaque of apatite called Randall’s plaque. The initial nidus is composed of apatite, and organic matrix is found in the basement membrane of thin descending loops of Henle. It then propagates to the interstitium of the renal papilla. Damage to the overlying epithelial cells exposes the plaque to the supersaturated urine and oxalate calcium stones grow. Hypercalciuria, reduced volume and acidic urinary pH all correlate with plaque formation. Although small amounts of plaque can be found in cases of apatite stones (i.e. brushite, secondary to distal tubular acidosis), the above mechanism is a common feature of idiopathic CaOx stone formers.

**Inhibitors and Promoters of Stone formation**

Various substances in the body have an effect on stone forming processes, thereby influencing a person’s ability to promote or prevent stone formation. Inhibitors are defined as substances that inhibit the nucleation, growth, aggregation, and cell attachment of crystals, thereby preventing stone formation. Promoters of stone formation facilitate stone formation. An imbalance between urinary promoting and inhibiting factors has been suggested as more important in urinary stone formation than a disturbance of any single substance. These substances include inorganic compounds, proteins, and glycosaminoglycans (Table 1). Abnormal function and or concentration of these compounds in the urine may modify physiochemical conditions to promote stone formation.

**Table 1: Stone promoting and inhibiting factors**

<table>
<thead>
<tr>
<th>INHIBITING FACTORS</th>
<th>PROMOTING FACTORS</th>
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<tbody>
<tr>
<td><strong>Inorganic</strong></td>
<td>Calcium</td>
</tr>
<tr>
<td>Citrate</td>
<td>Sodium</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Oxalate</td>
</tr>
<tr>
<td>Pyrophosphate</td>
<td>Urate</td>
</tr>
<tr>
<td><strong>Organic:</strong></td>
<td>Cystine</td>
</tr>
<tr>
<td>Tamm-Horsfall protein</td>
<td>Tamm-Horsfall protein</td>
</tr>
<tr>
<td>Protease inhibitor: inter alpha inhibitor</td>
<td>Low urine pH</td>
</tr>
<tr>
<td>Urinary Prothrombin fragment 1</td>
<td></td>
</tr>
<tr>
<td>Glycosaminoglycans</td>
<td></td>
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<tr>
<td>Osteopontin (Uropontin)</td>
<td></td>
</tr>
<tr>
<td>Renal Lithosthatine</td>
<td></td>
</tr>
<tr>
<td>Other Bikunin, Calgranulin</td>
<td></td>
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<tr>
<td>High urine flow</td>
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</table>
**Inhibitors of Stone Formation**

Citrate is a substance that is found in urine and chelates calcium, making it unavailable for binding with oxalate and phosphate and thereby lowering urinary SS and preventing stone formation. Urinary citrate levels are highest in young children and decrease into adulthood, but relative hypocitraturia is a common finding in pediatric nephrolithiasis. Hypocitraturia has also been shown to be a risk factor for recurrent stone disease in children. Treatment with oral citrate supplementation has been shown to reduce stone risk. Although citrate is the best described inhibitor of stone formation, magnesium is also included in the discussion of kidney stone prevention. Although not as exhaustively researched as hypocitraturia, hypomagnesuria has been established as a risk factor for formation of calculi. In children, urinary magnesium excretion decreases with age when adjusted for creatinine excretion or body weight. Treatment with oral magnesium alone has not been shown to improve stone risk, although risk improves when combined with citrate supplementation. Other endogenous inhibitors of stone formation have been identified, including glycosaminoglycans, Tamm-Horsfall protein, pyrophosphate, nephrocalcin, and osteopontin. The mechanism by which they reduce kidney stone burden is through bonding with crystal surface calcium, thereby getting in the way of crystal aggregation.

**Promoters of Stone formation:**

On the cell surfaces of the kidney, cell debris, protein aggregates and other crystals may provide analogous site for nucleation. These nucleation sites may lower the SS required to initiate crystallization and therefore promote CaOx crystallization. The supersaturation (SS) of CaOx is primarily determined by the concentrations of calcium and oxalate in the urine, whereas SS CaP is primarily determined by urinary calcium concentration and urinary pH; both SS CaOx and SS CaP are affected inversely by citrate concentration. Another common lithogenic factor is low urinary volume, found in the majority of idiopathic stone-formers. Urine pH plays a role in stone risk as well. Low urine pH is the major determinant of risk for uric acid stones, whereas high pH is associated with CaP stones. Stasis of the urinary tract, with or without frank obstruction, is an important contributor. Last, urinary tract infection used to play a significant role in pediatric nephrolithiasis as the major cause of ammonium magnesium phosphate (struvite) stones. This role has diminished with improved diagnosis and treatment of urinary tract infections.

Among children who do form stones, predisposing metabolic factors, infection, and/or urinary stasis are identified in the majority. Predisposing factors should be systematically sought in every pediatric or adolescent patient with stones, since such factors form the basis of effective treatment interventions.
4. Types of Kidney Stones in Children

Frequency of stone composition based on several pediatric series are calcium oxalate in 40–60%, calcium phosphate in 15–25%, magnesium ammonium phosphate (struvite) in 17–30%, cystine in 6–10%, and uric acid in 2–10%.

4a. Calcium-containing stones

This is the most common type of kidney stones with an incidence of 70-80%. There are two main types of calcium-containing stones: calcium oxalate and calcium phosphate.

A. Calcium oxalate stones

Supersaturation of urine with calcium oxalate may result from elevated excretion of calcium, oxalate, or uric acid; or due to hypocitraturia.

i) Hypercalciuria:

The prevailing abnormality among children with calcium stones is hypercalciuria, accounting for 50–97% of those with an identifiable metabolic etiology. The commonly accepted definition is a urinary calcium excretion greater than 4 mg/kg/day, or a urinary calcium/creatinine (U Ca/Cr) ratio higher than 0.21. This can be primary or secondary to hypercalcemic states. Several rare congenital monogenic disorders can also induce hypercalciuria with subsequent nephrocalcinosis and stone formation (Table 2). The majority of calcium oxalate stone formers present increased urinary calcium that cannot be attributed to any known cause. Idiopathic hypercalciuria is characterized by the presence of normal plasma calcium and is traditionally classified into three subtypes: Absorptive hypercalciuria (AH) is defined by a normal fasting U Ca/Cr (<0.20 mg Ca/mg Cr) that significantly increases following a calcium load (>0.20 mg Ca/mg Cr). Up to 40% of children with AH have a family history of nephrolithiasis, suggesting a genetic predisposition. An additional mediator of AH may be 1,25-dihydroxyvitamin D, as elevated concentrations have been reported in hypercalciuric children increased urinary calcium excretion due to increased intestinal absorption; Renal leak hypercalciuria, i.e. a primary tubular defect leading to decreased calcium re-absorption; and Resorptive hypercalciuria, i.e. a primary increase in bone mineral turnover. Beyond this organ-specific classification, idiopathic hypercalciuria is rather a state of increased calcium metabolic turnover where the above-mentioned alterations coexist. The exact pathogenic mechanisms are unclear and include: increased levels of vitamin D or vitamin D receptors (VDRs) with a subsequent increased tissue response or a defect in renal re-absorption of calcium and phosphorus, possibly in the proximal tubule. Environmental factors, such as ingestion of high sodium or ketogenic diets, also promote calcium excretion. Finally, any hypercalcemic condition may cause hypercalciuria by increasing the calcium filtered load as well as directly inhibiting renal calcium absorption.
Table 2. Classification of hypercalciuria

<table>
<thead>
<tr>
<th>1. Idiopathic</th>
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<tbody>
<tr>
<td>Absorptive hypercalciuria</td>
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<tr>
<td>Renal leak hypercalciuria</td>
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<tr>
<td>Resorptive hypercalciuria</td>
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</tbody>
</table>

<table>
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<tr>
<th>2. Secondary to hypercalcemic states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Hypervitaminosis D</td>
</tr>
<tr>
<td>Prolonged immobilization</td>
</tr>
</tbody>
</table>

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<tr>
<th>3. Congenital monogenic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dent’s disease</td>
</tr>
<tr>
<td>Bartter’s syndrome types I, II, III, V</td>
</tr>
<tr>
<td>Autosomal dominant hypocalcemic hypercalciuria</td>
</tr>
<tr>
<td>Familial hypomagnesemia with hypercalciuria and nephrocalcinosis</td>
</tr>
<tr>
<td>Distal renal tubular acidosis</td>
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</tbody>
</table>

### ii) Hyperoxaluria:

Urinary oxalate is equally important to calcium in supersaturation. Hyperoxaluria can be the result of primary overproduction, increased dietary consumption or enhanced intestinal absorption (Table 3). Oxalate is produced in the liver from glyoxalate metabolism. Normally, in hepatic peroxisomes, glyoxalate is metabolized to glycine and glycolate by alanine-glyoxylate aminotransferase (AGT) and glyoxalate reductase/ hydroxypyruvate reductase (GRHPR), respectively (Appendix-Figure 1). Inherited defects of these enzymes lead to oxalate overproduction. Primary hyperoxaluria is classified into three types with recessive autosomal inheritance. Type 1 is more common with an incidence of 1 per 100,000 live births. Diminished activity of hepatic alanine glyoxylate aminotransferase allows for accumulation of glyoxylate, which is metabolized to oxalate and glycolate. Increased filtered oxalate may result in luminal calculi composed of oxalate. It is characterized clinically by early onset with nephrocalcinosis, stone formation, renal failure and systemic deposition of oxalate (bones, joints, heart, vessels, peripheral nerves, and retina). Prognosis is poor with rapid progression to end-stage renal disease in young age. Type 2 is caused by a deficiency of glyoxalate reductase/ hydroxypyruvate reductase (GRHPR). It has milder clinical manifestations, typically causes nephrolithiasis only and rarely leads to renal failure. Type 3 has recently been identified as being caused by mutations in a novel gene HOGA1 (formerly DSDPSL gene) hypothesizing a gain of hepatic or renal mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA1) activity as the underlying metabolic source of excess oxalate. HOGA1 gene is located in chromosome 10q24.2.
Hyperoxaluria also results from increased intestinal absorption due to bowel disease. Calcium in the gastrointestinal tract typically binds free oxalate and both are then excreted. Malabsorptive states increase the luminal fatty acid content. The fatty acids are then free to complex and deplete luminal calcium, allowing for unbound oxalate to be absorbed. Epithelial damage induced by increased bile and free fatty acids may augment oxalate absorption. Hyperoxaluria can also result from ingestion of foods high in oxalate content or consumption of excessive ascorbic acid. Absorption of oxalate, in the absence of intestinal disease, may be exacerbated by low dietary calcium intake. A possible contributing factor may be depletion of Oxalobacter formigenes, a bowel bacterium that metabolizes oxalate. Oxalobacter formigenes is a gram negative anaerobic enteric bacterium which regulates oxalate homeostasis by utilizing oxalate for its biosynthesis and promoting oxalate secretion. Its absence from the intestinal lumen is associated with increased oxalate absorption and oxalate calcium nephrolithiasis. A suggested scheme for evaluating hyperoxaluria is shown in Appendix-Figure 2.

Table 3. Classification of hyperoxaluria

<table>
<thead>
<tr>
<th>1. Primary hyperoxaluria</th>
</tr>
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<tbody>
<tr>
<td>Type 1: deficiency of alanine-glyoxylate aminotransferase</td>
</tr>
<tr>
<td>Type 2: deficiency of glyoxalate/hydroxypyruvate reductase</td>
</tr>
<tr>
<td>Type 3: deficiency of 4-hydroxy-2-oxoglutarate aldolase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Dietary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestion of oxalate-rich food: chocolate, almond, nuts, spinach, tea</td>
</tr>
<tr>
<td>Hypervitaminosis C</td>
</tr>
<tr>
<td>Low dietary calcium and magnesium</td>
</tr>
</tbody>
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<table>
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<tr>
<th>3. Increased enteric absorption in malabsorptive syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Bacterial overgrowth syndromes</td>
</tr>
<tr>
<td>Gastric by-pass surgery, small bowel resection</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
</tr>
<tr>
<td>Chronic biliary diseases</td>
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</tbody>
</table>

### iii) Hypocitraturia:

Citrate is a naturally occurring inhibitor of calcium oxalate and calcium phosphate crystallization. Citrate is the dissociated anion of citric acid synthesized in mitochondria and enters into the tricarboxylic acid cycle. In plasma it forms complexes with the divalent anions calcium and magnesium and is filtered freely in the glomerulus. In the tubular lumen it binds calcium anions increasing their solubility and inhibits the nucleation of CaOx crystals. Furthermore, citrate impairs agglomeration of calcium oxalate
and impedes growth of calcium phosphate crystals. Citrate excretion is regulated by proximal tubule citrate absorption and metabolism. Both processes are stimulated by intracellular acidosis of the proximal tubule, caused by systemic metabolic acidosis, potassium depletion, or a ketogenic diet. The evaluation of metabolic acidosis should include consideration of renal tubular acidosis (RTA). While distal RTA typically induces hypocitraturia, proximal RTA is associated with normocitraturia despite systemic acidosis.

Whether or not citrate is a primary factor in stone formation in a particular patient, increasing a lower citrate concentration to a higher one can be beneficial in minimizing calcium stone forming activity. Citrate measured in the urine may be artifactually low in the presence of a urinary tract infection, and should be repeated after antibiotic treatment.

iv) Hyperuricosuria:
Hyperuricosuria imparts several effects on the urinary milieu that promote calcium stone formation. The primary mechanism is the salting-out phenomenon by which uric acid or sodium urate enhances calcium oxalate precipitation by lowering its solubility. Sodium urate crystals also induce heterogeneous nucleation of calcium oxalate, and hyperuricosuria can adsorb urinary inhibitors of calcium crystallization. Hyperuricosuria is found in 2–10% of children and adolescents with metabolic stones. Determining whether uric acid excretion is abnormal in children can be a challenge. Uric acid excretion is highest in infancy and remains high, relative to adult values, until adolescence. Normal levels of urinary uric acid are so high in infants that crystals may precipitate in diapers and be misidentified as blood. Idiopathic hyperuricosuria is an uncommon cause of nephrolithiasis and hematuria in children. Approximately 12% to 40% of children who have idiopathic hyperuricosuria have coexistent hypercalciuria. Mild idiopathic hyperuricosuria may be a cause of hematuria and is often found in conjunction with hypercalciuria. A defect in renal tubular transport of uric acid, either due to reduced proximal tubular reabsorption or to increased secretion may be found. Idiopathic renal hyperuricosuria is often familial and asymptomatic. Secondary hyperuricosuria may result from diets high in protein, or to ketogenic diets, and from medications including dicumarol, ascorbic acid, probenicid, phenylbutazone, salicylates, and citrate as well as pancreatic extract therapy in patients with cystic fibrosis. It can be seen in association with diabetes and the syndrome of inappropriate secretion of antidiuretic hormone.

B. Calcium phosphate stones
Calcium phosphate stones include apatite (carbapatite or hydroxyapatite) and brushite (calcium monohydrogen phosphate) stones with an occurrence rate of 4-10% and 2-6%, respectively. Promoting
Factors of calcium phosphate stone formation are hypercalciuria and alkaline urinary pH which induces supersaturation of monohydrogen phosphate and crystal precipitation. People with calcium phosphate stones have more numerous and often larger stones than people with calcium oxalate stones. Both types of calcium phosphate stones share similar chemical components, but their crystalline structure and clinical features differ. Brushite stones are very hard and do not break well with shock wave treatments. Hydroxyapatite crystals can plug the kidney tubules and injure kidney cells. Brushite stones appear more resistant to conservative therapy and usually need more extracorporeal shock wave lithotripsy (ESWL) treatments or even surgical intervention. There is an increase in the prevalence of the calcium phosphate contained in stones over time. This is associated with the number of ESWL treatments. ESWL-induced renal injury and consequent altered urinary acidification may contribute to alkalinization of urine pH and growth of calcium phosphate stones.

4b. Struvite stones

Struvite calculi (magnesium ammonium phosphate) result from infection with urease-splitting organisms that generate ammonium and bicarbonate via hydrolysis of urea. This ammonium-rich, high-pH environment promotes precipitation of magnesium and phosphate, thus creating struvite stones. A variety of bacterial species produce urease, including Proteus, Staphylococcus, Klebsiella, Providentia, Pseudomonas, Enterobacter, Ureaplasma urealyticum, Corynebacterium urealyticum, and some anaerobes. Struvite tends to form staghorn calculi that can grow rapidly and present as obstructive lesions or are identified because of associated infections and are challenging to treat. Management is hampered by poor penetration of antibiotics into the matrix where bacteria reside and evade antimicrobial effects. The structure of struvite calculi usually necessitates surgical removal, followed by prolonged administration of antibiotics. Just under half of the patients with infected staghorn calculi can be rendered stone free by ESWL, such that combined procedures including percutaneous nephrolithotomy are often needed. Retained stone fragments can serve as a nidus for early recurrence. Improvements in urologic surgical options for children have reduced the incidence of stones due to urinary tract infections. Struvite stones form only in the setting of infection because urease is exclusively a bacterial product that is not present in sterile urine. Early studies identified infection as the most frequent cause of nephrolithiasis in children. Although infection with urease producing organisms can itself produce nephrolithiasis, often the infection exacerbates underlying metabolic factors. Some studies have shown, in about 20–61% of patients with infection stones to have metabolic factors predisposing to stone formation. Stasis due to urinary tract abnormalities also predisposes to infection, further demonstrating the interaction among infection, metabolic factors, and structural abnormalities of the urinary tract in the genesis of calculi.
4c. Cystine stones

Cystinuria accounts for 2–8% of metabolic stones in children. Cystinuria is an autosomal recessive condition in which transport of dibasic amino acids by the proximal tubule is impaired. Cystine, ornithine, arginine and lysine all contribute to the dibasic aminoaciduria. However, because of its poor solubility at normal or low urinary pH, only cystine results in urinary precipitation and recurrent calculi, e.g. at a pH of 7, the solubility threshold of cystine is 1 mmol (243 mg)/L and at pH of 7.5 it is 2 mmol/L. Characteristic hexagonal crystals can sometimes be seen in the urine of patients with cystinuria. Cystine solubility is enhanced at an alkaline urine pH, such that alkanization of the urine is an important component of treatment regimens. However, even at an optimal urine pH of 7, cystine solubility in the urine is limited to approximately 1 mmol/L of urine. The prevalence of cystinuria in the general population in the United States and Europe is estimated at 1 in 7000, but varies widely in various parts of the world ranging from 1/2500 in Jews of Libyan origin to 1/100,000 in Sweden. Although it is an autosomal recessive disorder with all homozygotes affected, some heterozygotes have aminoaciduria and subsequent symptoms. Due to immaturity of renal tubule function during infancy, and the complexity of compound heterozygosity, it is difficult to definitively establish the diagnosis of cystinuria prior to 1 year of age. Patients with homozygous forms of cystinuria frequently experience their first stone episode during childhood or adolescence and have recurring, life-long stone formation. The medical preventive management is the mainstay which is discussed in detail in the treatment section. Even with optimal medical management urologic procedures are periodically required. With advancing age, elevated serum creatinine concentrations can be encountered in 17–50% of patients, with a small proportion (approximately 3%) eventually requiring dialysis. A suggested scheme for evaluating cystinuria is shown in Appendix-Figure 3.

4d. Uric acid stones

Uric acid stones, or mixed uric acid and calcium oxalate stones, are most commonly seen in patients with concentrated acidic urine and in those with features of metabolic syndrome. The saturation of urine with respect to uric acid depends on uric acid content, urine pH, and urinary volume. Uric acid excretion is greater in children than in adults and varies with age. The highest fractional excretion is found in neonates and declines with age, reaching values similar to adults (10%) by adolescence. Because of high fractional excretion in children, normouricemia may occur despite excessive production, such as with disorders of purine metabolism. A recent follow-up study showed that gout, characterized by hyperuricemia, recurrent monoarthritis and hyperuricosuria independently increase the risk for incident kidney stones in men. Low urinary pH is the most common and by far the most important risk factor in uric acid nephrolithiasis. In the absence of hyperuricosuria, low urinary pH alone can convert urinary urate into the sparingly soluble
uric acid. The causes of low urinary pH in idiopathic uric acid nephrolithiasis are considered to be
defective ammonium excretion along with increased net acid excretion. Patients with an ileostomy are at
risk of uric acid stones because of high bicarbonate and fluid losses. Increased cell turnover, occurring for
example in myeloproliferative disorder and inflammatory bowel disease, is also associated with uric acid
stones. Measurement of urinary uric acid output is unhelpful because the solubility of uric acid in urine is
highly pH–dependent: at low pH, even small amounts will precipitate, whereas the reverse is true at high
pH.

4e. Kidney stones related to inborn metabolic diseases

Kidney stones may occur in many kinds of inborn metabolic disorders, either as the initial symptom (e.g.
primary hyperoxaluria, cystinuria) or as a late event (e.g. glycogen storage disease). Urine supersaturation
may be related to the biochemical defect itself (oxalate, cystine) or to a secondary disorder (urate, citrate).
Nephrolithiasis associated with inborn metabolic diseases should be suspected in the presence of any of
the characteristics which include: onset of the disease during childhood, family history (consanguinity in
cases of recessive inheritance, urolithiasis among parents in cases of dominant inheritance), associated
tubular dysfunction, bilateral stones and/or nephrocalcinosis, multiple and recurrent stones, presence of
extra-renal involvement. Inborn errors of purine and pyrimidine metabolism and glycogen storage disease
type 1 will be discussed below as primary hyperoxaluria and cystinuria have already been discussed
above.

i) Inborn errors of purine and pyrimidine metabolism

Inborn errors of purine and pyrimidine metabolism may be associated with nephrolithiasis of various
composition and pathophysiology which include: Phosphoribosyl pyrophosphate synthetase superactivity
(PRPPS), hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency, adenine
phosphoribosyltransferase (APRT) deficiency and xanthine dehydrogenase/xanthine oxidase (XDH)
deficiency (Figure 2). All these lead to calculi which are primarily radiolucent, but they can be identified
by ultrasound. Most inborn errors of purine and pyrimidine metabolism are characterised by
hyperuricosuria, but they are also characterized by calcium stone formation. Many children with isolated
hyperuricosuria may present with hematuria without evidence of stones, but patients with inborn errors of
purine and pyrimidine metabolism exhibit extra-renal involvement, which is a major part of the prognosis
of the disease.

1. Phosphoribosyl pyrophosphate synthetase superactivity
Phosphoribosyl pyrophosphate (PRPP) synthetase superactivity is of X-linked inheritance. The disease usually seen in young male patients with gouty arthritis and uric acid nephrolithiasis, sometimes leading to ESRD. This x-linked disease also expresses in females. Plasma uric acid is increased and urine uric acid is also increased. Such uric acid overproduction may appear during infancy, together with neurological abnormalities, i.e. sensorineural deafness, hypotonia, motor delay, ataxia and autistic features. The enzyme forms PRPP from ribose-5-phosphate and adenosine triphosphate (ATP). PRPP synthetase is highly regulated; various genetic regulatory and catalytic defects may lead to superactivity, resulting in increased generation of PRPP. PRPP synthetase superactivity is one of the few examples of enhanced enzyme activity. The pathophysiology of neurological involvement is unknown. The diagnosis is based on kinetics studies of the enzyme on erythrocytes and cultured fibroblasts in a limited number of laboratories. The disease should be differentiated from partial HPRT deficiency, which may give similar clinical signs. The treatment is based on allopurinol, which inhibits xanthine oxidase and results in a decrease in the production of uric acid and its replacement by both hypoxanthine and xanthine, which are more soluble than uric acid. The initial dosage is 10–20 mg/kg per day for children and 2–10 mg/kg per day for adults, which should be further adjusted to the minimum required to maintain normal plasma uric acid concentration, and reduced for patients with impaired renal function. Additional measures to prevent crystallization are recommended: a low purine diet (free of organ meats, fish such as anchovy, herring, mackerel, salmon, sardines and tuna, dried beans and peas), high fluid intake and alkalinization aiming at a urinary pH of 6.0 to 7.0. Adequate control of plasma uric acid is required in order to control gout and renal involvement, but it has no influence on neurological outcome.

2. Hypoxanthine-guanine phosphoribosyltransferase deficiency: Lesch–Nyhan syndrome

Deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) activity lead to Lesch-Nyhan disease which is an inborn error of purine metabolism associated with uric acid overproduction and various degrees of neurological involvement, depending on the degree of enzyme deficiency. The gene is located on the X chromosome, (Xq2.6–2.7), and expression is almost exclusively recessive, but a small number of females have been reported. Phenotypic heterogeneity in clinical expression is seen and correlates with varying amounts of residual activity in the intact cell assay. The classic clinical picture combines neurologic features of retarded motor development, dystonia and involuntary movements, and self-injurious behavior with features that are consequences of the accumulation of uric acid. Hyperuricemia is characteristic as is uricosuria. An elevated uric acid to creatinine ratio is a useful initial screening test for this and other metabolic hyperuricemias. Normal children excrete less than 1mg uric acid/mg creatinine. Prompt assay of a fresh sample is preferable to a 24 h collection at room temperature because bacterial contamination may cause a spuriously low result. The clinical
consequences of hyperuricemia include gouty arthritis, tophi, hematuria, nephrolithiasis, urinary tract infection, and renal failure. A definitive diagnosis requires analysis of the activity of HPRT. In erythrocyte lysates activity approximates zero in classic Lesch–Nyhan disease. Treatment with allopurinol is effective in controlling hyperuricemia and its consequences. No medication has modified the neurological or behavioral manifestations of disease in classical Lesch–Nyhan patients. Bone marrow transplantation may restore erythrocyte HPRT, but it has no influence on neurological symptoms.

3. **Adenine phosphoribosyl transferase deficiency**

Another disorder of purine metabolism that leads to renal stone disease in children is adenine phosphoribosyltransferase (APRT) deficiency. The deficiency results in suppression of adenine, and adenine is oxidized by xanthine oxidase into 2, 8-dihydroxyadenine, which is a very poorly soluble compound. Such a deficiency can be complete or partial (only in Japanese patients). Adenine phosphoribosyl transferase (APRT) deficiency is of autosomal recessive inheritance, and the gene has been located on chromosome 16q24. All Japanese patients carry the same mutation, while approximately 30 mutations have been reported in Caucasians. The deficiency may lead to clinical manifestations in early childhood, but it can also remain silent for decades. Symptoms include the passage of crystals, gravel, and stones. Such nephrolithiasis is responsible for abdominal colic, dysuria, hematuria, urinary tract infection, and, sometimes, acute anuric renal failure. 2, 8-dihydroxyadenine is found in crystals and stones and can be distinguished from uric acid stones only by infrared spectrophotometry. The deficit is confirmed by assessment of APRT activity in red blood cells. Allopurinol should be given to patients with symptoms in order to inhibit the formation of 2, 8-dihydroxyadenine. In addition, dietary purine restriction and high fluid intake are recommended, but alkalinization of the urine is not advised, since the solubility of 2, 8-dihydroxyadenine is unchanged up to pH 9. The ultimate outcome depends on renal function at the time of diagnosis, and delayed identification of the disease may lead to chronic renal insufficiency. A suggested scheme for evaluating APRT deficiency is shown in Appendix-Figure 5.

4. **Xanthinuria (Xanthine dehydrogenase/Xanthine -oxidase deficiency)**

Hereditary xanthinuria is a rare autosomal recessive disorder of purine metabolism associated with urinary over excretion of xanthine. Affected patients often develop radiolucent urinary stones, crystalline nephropathy and even ESRD, although the disease course is often fairly benign. The prevalence of xanthinuria has been estimated to be around 1:6,000 to 1:69,000 of the general population. Classical xanthinuria has two forms: An isolated deficiency of XDH (Type 1 deficiency), or and type II patients have mutations in both the XDH and aldehyde oxidase genes AOX), both associated with reduced enzyme activity. In both cases xanthine accumulates since it can not be converted to uric acid due to diminished XDH activity. It is eliminated in urine where it is relatively insoluble and tends to form
stones. The diagnosis should be suspected in patients with radiolucent kidney stones and low serum uric acid levels. Typically urinary levels of xanthine are extremely high while urine uric acid levels are much reduced. A stone analysis of pure xanthine is diagnostic. Xanthine solubility is lower in acidic urine therefore alkalinization with potassium citrate to a target pH of 7 is a mainstay of therapy. Other helpful measures include generous hydration and dietary purine restriction.

ii) **Glycogen storage disease type 1**
Type 1-GSD, also known as von Gierke's disease, is an inborn error of metabolism characterized by a glucose-6 phosphatase deficiency. As a result of the incapacity to dephosphorylate glucose-6-phosphate, glucose production from glycogenolysis and gluconeogenesis is impaired and severe hypoglycaemia episodes can result. Nephrolithiasis is the most frequently described renal complication. Part of the glucose-6-phosphate excess is metabolized by pentose phosphate shunt, therefore leading to hyperuricaemia and urate kidney stones have been considered a major cause in nephrolithiasis in the past. In addition, renal distal tubular dysfunction can occur, even in patients with adequate metabolic control, and may lead to a combination of low citrate excretion and hypercalciuria. Normally, urinary citrate excretion increases with age, but, in patients with GSD-1a, both calcium and citrate excretion are inversely correlated with age. Such reduction in citrate excretion may be due to chronic lactic acidosis secondary to deficient glucose production. The long-term combination of chronic acidosis and hypercalciuria may explain the relevance of severe osteoporosis in adults with GSD-1a. Oral citrate supplementation may be able to prevent and ameliorate nephrocalcinosis and the development of nephrolithiasis. Sodium salts should be avoided, to limit additional calcium excretion. In addition, such patients should be given allopurinol to control plasma uric acid and thiazides, in order to control hypercalciuria and prevent worsening of osteoporosis.

4f. **Kidney stones secondary to other clinical conditions**
There are a number of clinical conditions associated with metabolic factors that predispose to stone formation of which common ones are discussed below:

i) **Obesity and the associated metabolic syndrome**
It is being increasingly recognized that obesity and the associated metabolic syndrome a risk factor for stone formation. Insulin resistance results in increased net acid excretion and impaired buffering caused by defective urinary ammonium excretion, with the combination resulting in abnormally acidic urine. This defect can result in increased risk of uric acid precipitation despite normouricosuria. Well reported in adult patients, this complication of obesity has now been recognized in early adolescence. In addition to metabolic effects of obesity, bariatric surgical procedures, which are increasingly performed in
adolescents and even younger children, are associated with hyperoxaluria, low urine volumes, and nephrolithiasis. Enteric hyperabsorption of oxalate related to malabsorption is the postulated cause. The hyperoxaluria can be marked and in some adult patients has led to renal failure due to oxalate nephropathy. The emerging epidemic of obesity in children and adolescents will likely lead to an increased prevalence of renal stone disease.

**ii) Medullary sponge kidney**

Medullary sponge kidney (MSK) is a renal development abnormality with ectasia and cystic formation in the medullary collecting ducts. The most significant complication of MSK is medullary nephrocalcinosis resulting in nephrolithiasis. In addition to the anatomic abnormalities of ectatic collecting ducts, metabolic factors including hypercalciuria, hypocitric aciduria, incomplete RTA, and increased urine pH have been variably observed in MSK with nephrolithiasis.

**iii) Intestinal malabsorption**

Chronic inflammatory bowel disease, other malabsorption syndromes (cystic fibrosis, celiac disease), and s/p bariatric surgery can cause hypocitric aciduria and hypomagnesuria due to loss of bicarbonate and magnesium in the stool, hyperoxaluria from enhanced enteric oxalate absorption, hyperuricosuria due to increased cell turnover, and low urine volume because of diarrhea, which together result in reduced inhibitor activity, low pH, and high solute concentrations in the urine. Calcium oxalate nephrolithiasis has been reported in 5.2–10.4% of young patients with cystic fibrosis and nephrocalcinosis has been observed in another 6.3%. Pancreatic insufficiency with fat malabsorption and resulting enteric hyperoxaluria are suggested by the clinical setting although no correlation could be established between the degree of fat malabsorption and the urine oxalate excretion in two studies. Deficiency of enteric Oxalobacter formigenes due to repeated courses of antibiotics has also been suggested as a risk factor for hyperoxaluria in this patient population. Pancreatic enzyme replacement and high protein diets may contribute to hyperuricosuria. Damage to renal tubules by antibiotic treatment has been implicated by some authors as a contributing cause with hypercalciuria following a renal phosphate leak.

**iv) Structural abnormalities of urinary tract**

Stasis of urine often accompanies structural abnormalities of the urinary tract, whether congenital or acquired. By compromising the normal continuous flow of urine from the upper urinary tract or interfering with regular and complete emptying of urine from the bladder, stasis promotes crystal retention and stone formation as well as infection. A wide range of structural abnormalities has been associated with nephrolithiasis including medullary sponge kidney, autosomal dominant polycystic kidney disease, calyceal diverticuli, ureteropelvic junction obstruction, horseshoe kidney, ureteroceles, primary megaureter, posterior urethral valves, and neurogenic bladder. Patients with myelodysplasia or spinal cord injury often have impaired bladder emptying, recurrent urinary tract infections, and
hypercalciuria from relative immobilization. The overall incidence of stones in children with structurally anomalous, obstructed, or infected urinary tracts is low, on the order of 1–5%. This suggests that while these factors are permissive, children who form stones may also have underlying metabolic abnormalities. Hypercalciuria, hyperoxaluria, or hypocitraturia have been identified in 66–80% of patients with structural abnormalities of the kidneys or ureters who also had nephrolithiasis and underwent metabolic evaluation. Accordingly, complete metabolic evaluation is just as important in children with structural abnormalities of the urinary tract or infected stones as it is in those without.

v) Medication Induced Nephrolithiasis

Medication-induced calculi represent 1–2% of all nephrolithiasis. The medications reported to produce nephrolithiasis do so due to either renal excretion of the medication or a metabolite which may exceed its solubility in the urine, or stones may form due to metabolic effects induced by the medication. Among poorly soluble molecules, drugs used for the treatment of HIV-infected patients, namely indinavir and sulfadiazine, have become the most frequent cause of drug-containing urinary calculi. Indinavir is filtered by the kidney, poorly soluble in the urine at a pH of greater than 5, and can precipitate as radiolucent stones. Distinctive birefringent crystals with plate and starburst structures are observed in 20–25% of patients receiving this antiretroviral agent. The indinavir crystals or small stones may also act as a nidus for calcium oxalate or calcium phosphate, and thus can also be associated with partially radiopaque stones of mixed composition. Dissolution of stone material may be observed with discontinuation of indinavir, increased fluid intake, and urine acidification. Other medications that can precipitate to form urinary tract stones are ceftriaxone, sulfonamides, ampicillin, amoxicillin, triamterene, guaifenesin, phenazopyridine, and oxypurinol. The second group includes drugs that provoke urinary calculi as a consequence of their metabolic effects. Carbonic anhydrase inhibitors, used for management of epilepsy and glaucoma, result in alkaline urine, reduced urine citrate, and hypercalciuria. Agents of this class, including zonisamide, topiramate, and dorzolamide have been reported to be associated with calcium phosphate and calcium oxalate nephrolithiasis in children and adolescents. Commonly used agents such as calcium supplements, vitamin D, and its analogues can be associated with hypercalciuria and can predispose to stone formation. Cyclosporine A has been associated with hypercalciuria. Here, diagnosis relies on careful clinical inquiry because physical methods are ineffective to differentiate between urinary calculi induced by the metabolic effects of a drug and common metabolic calculi. The incidence of such calculi, especially those resulting from calcium/vitamin D supplementation, is probably underestimated. Better awareness of the possible occurrence of lithogenic complications, preventive measures based on drug solubility characteristics and close surveillance of patients on long-term treatment with medications with lithogenic potential, especially those with a history of nephrolithiasis, should reduce the incidence of medication-induced nephrolithiasis.
5. Nephrolithiasis and Chronic Kidney Disease

The risk of renal insufficiency has been estimated at 1.7% in idiopathic calcium oxalate nephrolithiasis. In a group of 40 patients with a mean duration of cystinuric stone disease of 26 years, renal insufficiency was found in 30% of patients, though none had reached end stage renal disease. In cystinuria patients, stone-preventive treatment appeared effective in preserving renal function. Infection staghorn stones eventually are associated with end stage renal disease in 20–30% of adult patients with unilateral involvement and a higher percentage of those with bilateral stones. Several forms of more severe nephrolithiasis, such as primary hyperoxaluria, Dent’s disease, 2, 8 dihydroxy adeninuria and familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) are frequently associated with renal insufficiency or end stage renal disease. For these reasons, and despite the excellent response to treatment noted in most children with nephrolithiasis, long-term nephrologic care is indicated particularly for those with more complex forms of renal stone disease.

6. Genetics of kidney stone disease

Genetic abnormalities are among the risk factors for stone disease in children. Kidney stone in children is considered to be a multifactorial disease, however there are several rare Mendelian syndromes that can cause pediatric stone disease. The study of these disorders has provided important information for the understanding of the molecular bases of kidney stone. Therefore, we summarize some of the clinically relevant forms of genetic stone disease:

1. **Primary hypercalciuria:** Hypercalciuria is one of the most frequent risk factors for urinary stones. Idiopathic hypercalciuria is considered multifactorial with a complex interaction of environmental and individual factors. Up to 50% of patients have a positive family history and it seems that genetically driven factors play a larger role compared to the diet related risks. Activating mutations in CASR gene lead to the autosomal dominant syndrome of familial hypocalcemia with hypercalciuria. Hypocalcemia results from inhibiting active and passive calcium reabsorption in the ascending limb of Henle’s loop and parathyroid hormone secretion. CASR gene encodes for a plasma membrane G-protein-coupled receptor. This receptor is activated by binding calcium ions on its extracellular domain. Inactivating mutations of CASR lead to hypocalciuria and hypercalcemia. A variety of other genetic disorders lead to hypercalciuria including Dent’s disease which is discussed below and tyrosinemia which is a rare disease and manifests with impaired liver and renal function, aminoaciduria, hypercalciuria, and tubular acidosis.
2. **Cystinuria**: Cystinuria is an autosomal recessive trait with aminoaciduria and accounts for up to 10% of all urinary stones in children. With an overall prevalence of 1:7000, cystinuria is one of the most frequent genetic disorders. It is caused by defective transport of cysteine and the dibasic aminoacids ornithine, lysine, and arginine across the epithelial cells of the proximal renal tubules and small intestine. Three different types of cystinuria have been described with type I being completely recessive (homozygous proband excretes large amount of cysteine and heterozygous parents or other relatives excrete normal amounts of amino acid) and types II and III incompletely recessive (heterozygotes excrete greater than normal amounts of cysteine). Mutations in solute carrier family 3, member 1 gene (SLC3A1) cause type I and mutations in SLC7A9 attribute to types II and III cystinuria.

3. **Primary Hyperoxaluria**: Primary hyperoxalurias (PH) are autosomal recessive disorders characterized by increased urine oxalate due to inborn overproduction. In human, oxalate is synthesized mainly via glycosylate oxidation and overproduction may be due to aberrations at one of several steps in glycosylate metabolism. Individuals with PH are at risk for recurrent nephrolithiasis (deposition of calcium oxalate in the renal pelvis/urinary tract), nephrocalcinosis (deposition of calcium oxalate in the renal parenchyma), or end-stage renal disease (ESRD) with a history of renal stones or calcinosis. Age at onset of symptoms typically ranges from 1 to 25 years. Other clinical features of PH include heart block, Raynaud phenomenon, livedo reticularis, acrocynosis, spasm of large arteries, pathologic fractures, crystalline retinopathy, and optic neuropathy. There are different 3 types of PH due to mutations in different genes but PH type I is due to mutations in AGXT and accounts for 80-90% of PH cases. Type 2 is caused by a deficiency of glyoxalate reductase/hydroxypyruvate reductase (GRHPR). It has milder clinical manifestations, typically causes nephrolithiasis only and rarely leads to renal failure. Type 3 has recently been identified as being caused by mutations in a novel gene HOGA1 (formerly DSDPSL gene) hypothesizing a gain of hepatic or renal mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA1) activity as the underlying metabolic source of excess oxalate. HOGA1 gene is located in chromosome 10q24.2.

4. **Dent disease**: Dent disease is an uncommon form of Fanconi syndrome and is characterized by low molecular weight proteinuria and hypercalciuria. As a result of renal tubular disorder, Dent disease is also characterized by aminoaciduria, glycosuria, and phosphate wasting. Mode of inheritance of Dent disease is X-linked recessive with lack of male to male transmission. Inactivating mutations in CLCN5 are causative for Dent disease. A suggested scheme for evaluating Dent’s disease is shown in Appendix-Figure 6.

5. **Lesh-Nyhan syndrome**: As discussed above Lesch-Nyhan syndrome is characterized by severe motor dysfunction (most never walk), cognitive and behavioral disturbances, and uric acid
overproduction (hyperuricemia). HPRT1 is the only gene known to be associated with Lesch-Nyhan syndrome.

6. **Primary hypomagnesemia**: Primary hypomagnesemia, also named familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), is an autosomal recessive disorder and is characterized by renal magnesium wasting and hypercalciuria. Calcium stones and bilateral nephrocalcinosis can be complicated by nephrogenic diabetes insipidus, urinary tract infections, and distal tubular acidosis. Hypocalcemia and hypomagnesemia can result in spasms, tetany, seizures, paresthesias, muscle weakness, and permanent neurologic impairment beginning in the first 3 months of life. Ocular manifestations include chorioretinitis, keratoconus, macular colobamata, myopia, and nystagmus. Male infertility (oligospermia) and sensorineuronal hearing loss have also been reported. Primary hypomagnesemia is caused by mutations in paracellin-1 gene (PCLN-1). A suggested scheme for evaluating FHHNC is shown in Appendix-Figure 7.

7. **Clinical presentation and evaluation**

7a. **Clinical presentation**

Approximately 60% of children and adolescents diagnosed with stone disease present with pain (flank or abdominal), 30% with gross hematuria, 15% with dysuria, and another 15% may be asymptomatic with incidental radiologic finding on a radiologic study for another indication.

7b. **Evaluation and diagnosis**

Initial approach to a patient with stone disease is to establish the diagnosis and then to proceed with an evaluation to assess for any predisposing causes to stone development. Evaluation begins with a detailed history and physical examination, including careful inquiry regarding any family history of nephrolithiasis, arthritis, gout, or renal disease. Acute or chronic urinary tract infection must be excluded. Identification of stone composition greatly facilitates diagnosis and management. A suggested scheme for evaluating possible nephrolithiasis is shown in Figure 3.
Laboratory evaluation

In the Emergency Room, initial blood work should be obtained to evaluate renal function (serum urea nitrogen, creatinine) and include electrolytes, calcium, magnesium, phosphorus and uric acid. On rare occasions, urolithiasis can present as acute renal failure resulting from obstruction of both ureters or the ureter of a solitary kidney. A urine sample should be obtained for urinalysis and urine culture, if indicated. Macroscopic or microscopic hematuria has been observed in as many as 85% to 90% of children with nephrolithiasis. The presence of crystals can be strongly suggestive of specific types of stones (Fig 4). Increased urine pH higher than 6.0 potentiates the crystallization of calcium phosphate. Higher pH, higher than 7.0, is often indicative of urease-producing organisms and struvite stones. Urine pH lower than 6.0 will decrease solubility of cystine and uric acid, thus increasing the likelihood of
formation of these types of stones. The urinalysis also allows assessment of the specific gravity as a surrogate marker for urinary concentration and to indirectly assess patient’s fluid intake.

**Figure 4:** Urinary crystals: a. Urinary calcium oxalate crystals. The typical bipyramidal calcium oxalate dihydrate crystals (short arrows) and a large dumbbell calcium oxalate monohydrate crystal (long arrows) are both seen. b. Uric acid crystals shows pleomorphic rhombic or diamond shape. c. Triple phosphate crystals, “coffin lid” crystals. d. Typical small- and medium-sized 2,8-dihydroxyadenine crystals. The medium-sized crystals are brown with dark outline and central spicules. e Urinary cystine crystals: The typical 6-sided crystal is diagnostic of cystinuria.

**Diagnostic Imaging**

Kidney stones may be diagnosed through abdominal x-rays (KUB), CT scans, ultrasounds or through an intravenous pyelogram (IVP). Approximately 80 percent of kidney/ureteral stones are calcified and can be seen on x-ray. Stones that contain calcium, such as calcium oxalate and calcium phosphate stones, are easiest to detect by radiography. Less radiopaque calculi, such as pure uric acid stones and stones composed mainly of cystine or magnesium ammonium phosphate, may be difficult, if not impossible, to detect on plain-film radiographs. Although IVP is a reliable test for kidney/ureteral stones, currently it is not commonly done due to risk of complications (e.g., exposure to radiation, adverse reaction to intravenous dye).
Clinical practice guidelines and evidence support using ultrasound for initial diagnostic imaging in children with suspected nephrolithiasis, and reserving CT for those with a nondiagnostic ultrasound in whom the clinical suspicion for stones remains high. The noncontrast spiral CT is the most sensitive and specific radiologic test, facilitating fast, definitive diagnosis. Adding contrast to the CT scan study may sometimes help clarify a difficult or confusing case, but, in general, contrast obscures calcific densities, and, as such, contrast scans are usually indicated only during subsequent evaluation of patients with stones.

Although ultrasound is less sensitive and specific than CT, ultrasound accurately identifies clinically significant kidney stones in children. Ultrasonography has the advantage of visualization of radiolucent as well as radiopaque stones, detection of hydronephrosis, and the absence of radiation exposure and is preferred for most routine follow-up assessments. However, lack of sensitivity for small stones, difficulty in comparing size of individual stones over time, lower sensitivity for visualization of ureteral stones, and the possibility of obstruction in the absence of hydronephrosis will, at times, dictate other imaging modalities. Passerotti et al studied 50 patients younger than 18 years with suspected nephrolithiasis and determined the diagnostic performance of ultrasound in accurately localizing kidney stones. Using CT as the gold standard, the sensitivity and specificity of ultrasound were 76% and 100%, respectively, when the radiologists interpreting the ultrasounds were blinded to CT results. In this population the positive predictive value of ultrasound was 96% and the negative predictive value was 62%. The average size of missed stones was 2.3 mm; moreover, of 50 cases assessed, only 4 had a clinical impact. Furthermore, in these 4 cases, ultrasound suggested the need for further imaging, which would have led to the diagnosis of distal ureteral stones. The authors concluded that despite the increased sensitivity of CT scan over ultrasound in stone detection, this difference may not be clinically significant. Similarly Johnson et al found that ultrasound correctly identified 89% of stones requiring surgical intervention.

Noncontrast CT has nearly 100% sensitivity and specificity to identify kidney stones. However, CT delivers ionizing radiation, which is associated with an increased risk of cancer. Although the attributable risk of cancer from a single CT performed for kidney stones is small (0.2% to 0.3% above baseline), the cumulative risk is higher for those undergoing repeated studies. Additionally the risk may be greater in children than in adults because of a longer life expectancy and greater sensitivity of developing tissues to the effects of radiation. Given the good sensitivity of ultrasound in detecting clinically significant stones and the radiation risk associated with CT, the American Urological Association in 2012 and the European Association of Urology in 2013 developed imaging recommendations for children with suspected
nephrolithiasis. Both groups recommend ultrasound as the first-line imaging modality, with noncontrast CT reserved for cases where ultrasound is nondiagnostic.

**Figure 5:** Renal calculus on a real ultrasound

**Figure 6:** Renal calculus on unenhanced computed tomography (CT)
Metabolic Evaluation

The goal of performing a metabolic evaluation is to identify abnormalities for which targeted therapies can be prescribed to decrease the risk of recurrent stones. The general consensus is that a complete metabolic evaluation should be performed in children with a first stone occurrence, because up to 70% of children with nephrolithiasis will have abnormalities in the urine that increase the risk of stone formation and may be targets for dietary and pharmacological interventions. Hypercalciuria and hypocitraturia, both of which increase the risk of recurrent kidney stones, are the most commonly identified metabolic abnormalities. Other risk factors include hyperuricosuria and hyperoxaluria. Stone analysis often allows the nephrologist to quickly narrow down the possible stone risk factors. For instance, a stone that is found to be calcium oxalate will allow the clinician to rule out cystinuria as the cause; it does not, however, discern whether this occurred from hypercalciuria, hyperoxaluria, or hypocitraturia. More typically, stone analysis is unavailable, making the cause of stone formation an inferential one based on a 24-hour urine collection. Metabolic evaluation ideally is performed while the patient is at home, consuming his or her regular diet, and free of infection. Although 24-hour urinary collections form the criterion for most urinary measurements (Table 4 and 5), obtaining such collections from small children can be difficult or impossible. Standards based on single specimens have been developed (Table 6). If no stone is recovered or analysis reveals a stone of calcium oxalate or calcium phosphate, a broad evaluation is required. Evaluation should begin with two 24-hour urine collections if possible, including measurement of volume, calcium, creatinine, oxalate, uric acid, sodium, citrate and supersaturation profiles of calcium oxalate, calcium phosphate and uric acid. Urinary cystine levels should be obtained with the first specimen. Unlike in adults, all these values should be indexed to weight, body surface area and creatinine level to be properly interpreted in children. Additionally 24-hour creatinine excretion should be quantified to determine the adequacy of the collection (normal 15 to 25 mg/kg/24 hours).

Once nephrolithiasis is diagnosed, additional blood work including serum parathyroid hormone levels, vitamin D levels, parathyroid hormone related peptide are indicated if the patient has hypercalciuria, hypercalcemia, or hypophosphatemia. Identification of stones composed of struvite, cystine, or uric acid narrows the differential diagnosis, allowing a more focused evaluation. Struvite stones always are associated with infection by a urea-splitting organism. Alternatively, the finding of a nonstruvite stone in the setting of infection suggests that the infection was secondary, and the search for a primary cause of nephrolithiasis should continue. Calcium excretion increases during pyelonephritis, so metabolic studies should be performed after any infections are resolved.
### Table 4. Normal urinary values in 24 h urine collection for all age children *(modified from various resources)*

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td></td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>&lt;5 mg/kg/day</td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>&lt;4 mg/kg/day</td>
</tr>
<tr>
<td>Oxalate</td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>&lt;0.5 mmol/1.73 m²/day</td>
</tr>
<tr>
<td>1 mo - 8y</td>
<td>1.2 / 0.4 mg/kg/day</td>
</tr>
<tr>
<td>8 - 12 y</td>
<td>1 / 0.5 mg/kg/day</td>
</tr>
<tr>
<td>&gt;12 y</td>
<td>0.6 / 0.2 mg/kg/day or &lt;40 mg/1.73 m²/day or &lt;0.5 mmol/1.73 m²/day</td>
</tr>
<tr>
<td>Cystine</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>&lt;24-48 mg/day or &lt;60 mg/1.73 m²</td>
</tr>
<tr>
<td>Cystine/Creatinine (mmol/g)</td>
<td>&lt;100 mmol/g creatinine</td>
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<tr>
<td></td>
<td>Homozygotes: &gt; 1200 mmol/g creatinine</td>
</tr>
<tr>
<td></td>
<td>Heterozygotes: 300-700 mmol/g creatinine</td>
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<tr>
<td>Citrate</td>
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<tr>
<td>Girls</td>
<td>&gt;300 mg/g creatinine</td>
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<tr>
<td>Boys</td>
<td>&gt;125 mg/g creatinine</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt;180 mg/g creatinine</td>
</tr>
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<td>Uric Acid</td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>40 / 17 mmol/kg/day</td>
</tr>
<tr>
<td>&lt;8y</td>
<td>11 / 5 mg/kg/day</td>
</tr>
<tr>
<td>8 - 12 y</td>
<td>10 / 5 mg/kg/day</td>
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<tr>
<td>&gt;12y</td>
<td>7 / 4 mg/kg/day or &lt;815 mg/1.73 m²/day</td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>0.4 / 2 mg/kg/day</td>
</tr>
<tr>
<td>&lt;8 y</td>
<td>2.5 / 1 mg/kg/day</td>
</tr>
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<tr>
<td>&gt;12 y</td>
<td>1.8 / 1 mg/kg/day</td>
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<td>Phosphorus</td>
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</tr>
<tr>
<td>Newborns</td>
<td>5-50 mg/kg/day</td>
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<tr>
<td>&lt;8y</td>
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<td>Neonate</td>
<td>8-12 mg/kg/day</td>
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<tr>
<td>1 mo - 1y</td>
<td>12-14 mg/kg/day</td>
</tr>
<tr>
<td>1 - 5 y</td>
<td>20 mg/kg/day</td>
</tr>
<tr>
<td>&gt;7 y</td>
<td>23-27 mg/kg/day</td>
</tr>
</tbody>
</table>

### Table 5. Normal urinary values in 24 hr urine collection in *school-age children* *(modified from Ped in Rev, 25, 2004)*

<table>
<thead>
<tr>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Oxalate</td>
</tr>
<tr>
<td>Cystine</td>
</tr>
<tr>
<td>Citrate</td>
</tr>
<tr>
<td>Uric acid</td>
</tr>
<tr>
<td>Volume</td>
</tr>
</tbody>
</table>
Table 6: Normal values – random urine (modified from Ped in Rev, 25, 2004)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>mg/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium/Creatinine</td>
<td>&lt;6 mo</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td></td>
<td>6-12 mo</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td></td>
<td>2-18 y</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Oxalate/Creatinine</td>
<td>0-6 mo</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td></td>
<td>6 mo-4 y</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td></td>
<td>4 y – 18 y</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Cystine/Creatinine</td>
<td>All ages</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Citrate/Creatinine</td>
<td>All ages</td>
<td>&gt;0.51</td>
</tr>
<tr>
<td>Uric acid/GFR (all values mg/dL calculated)</td>
<td>&gt;3 y</td>
<td>&lt;0.56 uric acid/dL of GFR</td>
</tr>
</tbody>
</table>

8. Management

8a. Acute management:

Medical management:

Supportive care: If the patient is symptomatic with severe renal colic, initial care includes pain control and aggressive hydration. Hospital admission is indicated when children have intractable pain or vomiting, infection with obstruction, or a single or transplanted kidney. Acute Stone Emergency Center Protocol used at Texas Children’s Hospital is attached in appendix-Figure 8.

Pain control: Pain associated with renal colic is best treated with narcotic analgesics combined with nonsteroidal anti-inflammatory medications if renal function is normal, specifically morphine and ketorolac.

Hydration: Intravenous hydration at 1.5 to 2 times the maintenance rate should be started as quickly as possible. Nausea and vomiting should be treated with intravenous antiemetics.

If any suspicion of urinary tract infection based on symptoms or urinalysis findings, start empiric antibiotic therapy after sending urine culture.

Patients with less severe disease who can be managed as an outpatient, oral NSAIDs can be used if renal function is not impaired. Outpatient observational treatment should include aggressive hydration with oral fluids such as water, fruit juice, milk, and tea.

Medical expulsive therapy: Once the diagnosis of nephrolithiasis is established, decision on whether the patient can pass the stone spontaneously or surgical intervention is required would depend on the size of
the stone and its orientation, with stones up to 4 mm having a high likelihood of spontaneous passage in children of all ages. With adequate pain control, uncomplicated unilateral stones causing only minimal or partial obstruction can be managed conservatively for several weeks before surgical intervention is considered.

During this period of observation, medical expulsive therapy (MET) for smaller stones has also been used, especially in older children, with some success, although evidence to support this form of therapy in pediatrics is limited. Either alpha-blockers or calcium channel blockers can be used to facilitate the passage of distal ureteral stones of size <10 mm. Medical expulsive therapy also has a role as adjunctive treatment after shock wave lithotripsy (SWL) or ureteroscopy, if stone fragments remain.

There have been few studies on patient and stone characteristics that predict whether a ureteral stone will pass spontaneously in children. However, similar to stones in adults, it stands to reason that smaller, distal ureteral stones are more likely to pass than larger, more proximal stones. For those stones in which spontaneous passage is deemed possible (usually smaller than 10 mm) with MET, the use of alpha-blockers or calcium channel blockers, may increase passage of ureteral stones and thus obviate the need for surgical intervention. Interest in these agents stems from the understanding that ureteral smooth muscle contraction is driven by an increase in intracellular calcium and is modulated by the autonomic nervous system. The alpha adrenergic and calcium channel blockers dilate the ureter due to high densities of alpha1a, alpha1d, and calcium channel receptors in smooth muscle of the distal third of the ureter and ureterovesical junction, therefore facilitates stone passage. Two meta-analyses of randomized controlled trials have been performed in adults. Both studies demonstrated that tamsulosin and nifedipine increased passage of ureteral stones. In adults alpha-blockers also proven to decrease time to stone passage and reduce analgesic requirements, and are cost effective relative to analgesics alone.

Evidence regarding the efficacy of MET in children is based on 4 studies that have tested whether MET increases the passage of ureteral stones in children. Aydogdu et al conducted a clinical trial and randomly assigned 39 children with distal ureteral stones that were smaller than 10 mm to either ibuprofen or doxazosin plus ibuprofen at a daily dose of about 0.03 mg/kg. There were no differences between the doxazosin and ibuprofen groups in the rate of stone passage (84 versus 70 percent) or in the mean time for stone expulsion (5.9 versus 6.1 days). Erturhan S et al performed a randomized control trial, including a total of 45 patients with a single lower ureteral stone, children were randomized to group 1 only ibuprofen and group 2: ibuprofen and doxazosin. Stone expulsion rate was higher for those received doxazosin plus ibuprofen (28.5% in group 1 vs 70.8% in group 2, p<0.001). Doxazosin treated group also had less colic
attacks and less time to stone expulsion. Mokhless et al performed a prospective cohort study in which children with distal ureteral stones received tamsulosin (0.2 mg daily at bed time for children <4 yrs and 0.4 mg for children >4yrs) and ibuprofen or ibuprofen and placebo. More stones passed in the tamsulosin cohort (88%) vs the placebo group (64%, p <0.01), the time to passage was also shorter in those receiving tamsulosin (8 vs 14 days, p <0.001) and need for analgesia was also less in treatment group (0.7 vs 1.4, p<0.02). Tasian et al also demonstrated similar efficacy of tamsulosin for ureteral stones smaller than 10 mm in a multi-institutional retrospective cohort study, the stone expulsion rate was higher in the tamsulosin cohort (56%) vs analgesics alone cohort (44%, p < 0.03). The adjusted odds of stone passage were 3.31 times higher in children prescribed tamsulosin (OR 3.31, 95% CI 1.49-7.34). Safety and effectiveness of doxazosin have not been established in children, whereas tamsulosin (Flomax) is safe in pediatric patients and is recently approved by US Food and Drug Administration for pediatric use, hence it would be appropriate to consider tamsulosin as the first line agent for MET when indicated.

**Stone retrieval:** The family/patient should be instructed to strain the child's urine for several days, in order to retrieve the stone. If the stone or any fragment is recovered, it should be sent for stone analysis. The known composition of the stone can guide further evaluation and preventive measures to prevent recurrent stones.

**8b. Surgical management:**

Appropriate surgical technique will be decided by the Urologist based on stone size and location.

**Extracorporeal shockwave lithotripsy (ESWL):** Extracorporeal shockwave lithotripsy is used with stones in various locations but is limited with larger lower pole stones, staghorn stones, and with the anatomically abnormal urinary tract. Extracorporeal shockwave lithotripsy is now used frequently in children and is considered by many as the first-line interventional therapy. Adverse effects of ESWL include renal hematoma, flank pain, hematuria, and trauma to tissues in the path of the lithotripter including skin bruising, pulmonary contusion, and pulmonary infiltrate. Most adverse effects are self-limiting. Overall, ESWL is an effective and fairly safe therapy for renal stones that are not appropriately or effectively treated by medical therapy, although it is not optimal for certain stone types and stone locations and has some adverse effects.

**Percutaneous nephrolithotomy (PCNL):** Percutaneous nephrolithotomy is useful for large, lower pole stones, and staghorn stones. Percutaneous nephrolithotomy involves percutaneous access to the renal pelvis with nephroscopic manipulation of the stone, which breaks it down so it can be extracted. Its use has become more common in pediatrics with the advent of smaller instruments. Percutaneous nephrolithotomy can be coupled with ESWL or other therapies to increase effectiveness. Percutaneous nephrolithotomy can be an appropriate therapy for larger stones that are not effectively treated by ESWL.
Most commonly reported complications after PCNL consist of significant bleeding (requiring transfusion), infection, and persistent urinary leakage. In general, PCNL is useful for larger stone burden that can still be managed without open surgical technique but may have significant associated blood loss. It is less invasive than open technique and generally has a shorter postoperative hospital course.

**Endoscopy:** Endoscopy is commonly used for distal ureteral calculi. Endoscopic management has become increasingly more common in pediatric patients and is considered first line by some, although it is considered only in older patients and in those in whom other therapies have failed. Endoscopy seems to be more useful when stones are less than 15 mm. Reported, but uncommon, complications include perforation requiring stent placement and distal ureteral stricture. Children with complex anatomic urologic abnormalities are not well suited for endoscopy.

**Open surgical approach:** Open surgery, once considered the primary therapy for pediatric stone disease, is now rarely used. The open surgical approach is generally reserved for failure of all other methods, including laparoscopy. The open approach may be needed for children with large stones who also have nonfunctioning kidneys. The open approach may also be considered in children with a congenitally obstructed system that also requires surgical correction or for children with very large bladder stones related to an anatomic abnormality.

### 9. Prevention of Recurrence:

Nephrolithiasis in children and adolescents, like that in adults, frequently recurs. The recurrence rate of nephrolithiasis varies from 24% to 33%. Recurrence rates are higher in children with demonstrable metabolic abnormalities. All patients in whom a metabolic risk factor for stone formation is detected should receive dietary and lifestyle modification.

**All Stone Formers**

**Fluid Intake**

Similar to adults, irrespective of the stone type or the metabolic risk factor, increased fluid intake is recommended for all children with stone disease. Aggressive fluid intake lowers the tubular concentration of all substances prone to precipitate in the tubules. In general, fluid intake of 1.5 times “maintenance” fluids is used; this translates to approximately 3 L of fluid intake for a teenager with stone disease to maintain a daily urine output of at least 2 L in adolescents. Alternative way to calculate amount of fluid required to account for the size of child is to use body surface area and to use a minimum of 2 L/m². Patients should increase fluid intake even more during hot weather or strenuous exercise. Water is preferable; use of other beverages may lead to undesirable increases in caloric or caffeine intake.
Consumption of fructose containing drinks increases urinary excretion of calcium and oxalate and thereby may increase stone risk. Consumption of fructose is highest in those younger than 30 years and a quarter of adolescents consume at least 15% of their calories from fructose, those with history of nephrolithiasis should be counseled to increase water intake to maintain a daily urine output of at least 2 L in adolescents and reduce sugary drink intake.

**Hypocitraturia**

Citrate inhibits calcium stone formation by complexing with calcium, thus decreasing the supersaturation of calcium in urine, and also by directly inhibiting crystal growth and aggregation. Hypocitraturia has been observed in approximately 60% of children with nephrolithiasis, making it an attractive modifiable risk factor for patients who form calcium based stones. The cornerstone of pharmacotherapy for patients with hypocitraturia and calcium oxalate nephrolithiasis is alkali therapy, usually in the form of potassium citrate.

- A diet high in fruit and vegetables is recommended because the high potassium content promotes urinary citrate excretion. These foods are also a source of phytates which, like citrate, increase calcium salt solubility.
- A diet high in animal protein reduces the excretion of citrate in urine. Regardless of stone risk, children should consume 100% of the recommended daily allowance of protein for their age.
- Potassium citrate is indicated in hypocitraturia and is also used as a urine alkalinizing agent. Recommended dose in children is 1 mEq/kg potassium citrate per day divided into 3 doses after meals. Doses are titrated to achieve an ideal urine pH 7. A higher pH exposes patients to the risk of calcium phosphate stones, particularly in the presence of hypercalciuria.
- Addition of amiloride may boost citrate excretion by its potassium-sparing effect.
- Efficacy of alternative sources of citrate supplementation like lemon or lime juice has not been examined in children. In adults lemonade consumption has shown to increase urinary citrate.
- Calcium phosphate stones do not occur as commonly as calcium oxalate stones. In contradistinction to calcium oxalate stones, these stones thrive not in acidic, but in basic conditions. Treatment is therefore acidification of the urine. This can be achieved through cranberry extract. A diet rich in whole grains has been shown to acidify urine, and contains little of the phosphorous plentiful in animal protein.
**Hypercalciuria**

**Sodium Restriction**

- A high sodium diet increases the calcium excretion and increase the risk for stone formation. High concentrations of calcium in the urine combine with oxalate and phosphorus to form stones.
- Daily sodium intake less than 2 to 3 mEq/kg for young children and less than 2.4 gm in adolescents and adults is recommended for patients with hypercalciuria or calcium based stones.
- Some common tips of sodium reduction: do not add salt or seasonings that contain sodium to food while cooking or after food has been prepared. Learning the sodium content of foods can help people control their sodium intake. Food labels provide information about sodium and other nutrients. Keeping a sodium diary can help a person limit sodium intake to 2.4 gm. When eating out, people should ask about the sodium content of the foods they order.
- Some foods have such large amounts of sodium that a single serving provides a major portion of the RDA. Foods that contain high levels of sodium include: processed food items, boxed meals, canned products, salted crackers, pickles/olives, fast foods etc.
- Food labels should be checked for ingredients and hidden sodium, such as: monosodium glutamate, or MSG, sodium bicarbonate, the chemical name for baking soda, disodium phosphate, sodium alginate and sodium nitrate or nitrite.

**Calcium intake**

- Calcium from food does not increase the risk of calcium oxalate or calcium phosphate stones and hence decreasing or limiting calcium intake is not recommended.
- Calcium in the digestive tract binds to free oxalate from food and prevent hyperoxaluria. Patients with calcium oxalate stones should include 800 mg of calcium in their diet every day, not only for kidney stone prevention but also to maintain bone density. A cup of low-fat milk contains 300 mg of calcium. Other dairy products such as yogurt are also high in calcium. For people who have lactose intolerance and must avoid dairy products, orange juice fortified with calcium or dairy with reduced lactose content may be alternatives.
• Calcium supplements may increase the risk of calcium oxalate stones if they are not taken with food.

**Protein intake**

• Meals high in animal protein result in an acid load that increases urine calcium and decreases urine citrate. Additionally animal protein, through the intake of purines, increases urinary uric acid.
• Regardless of stone risk, children should consume 100% of the recommended daily allowance of protein.

**Thiazides**

• Thiazides are used after maximizing urine calcium reduction by limiting dietary sodium intake.
• Thiazide diuretics (eg hydrochlorothiazide and chlorthalidone) are the first-line drugs for children with calcium stones and hypercalciuria. Through volume contraction thiazides increase calcium absorption in the proximal tubule and thereby decrease urine calcium.
• Thiazides should be avoided in patients with coexisting hypercalcemia.

**Hyperoxaluria**

• Increase fluid intake (as indicated above). As in all types of kidney stone disease, a high volume dilute urine is desirable in enteric hyperoxaluria. However, in patients with short bowel, a high water intake can exacerbate diarrhea without improving urine dilution. A solution containing electrolytes and sugar may be preferable to plain water.
• Avoid excess vitamin C supplementation, due to its metabolism to oxalate.
• Those with hyperoxaluria secondary to a malabsorption syndrome (eg, CF or inflammatory bowel disease) require disease specific treatment so as to counteract the steatorrhea which has resulted in the hyperoxaluria state.
• Although hyperoxaluria is a risk factor for calcium oxalate stone formation, less than 20% of urinary oxalate excretion is due to dietary sources. Accordingly the strength of evidence that reducing oxalate consumption decreases stone risk is low, although a randomized clinical trial in adults showed that dietary oxalate restriction reduced urinary oxalate excretion. However, given the generally weak evidence that oxalate restriction decreases the risk of recurrent stone formation in adults and the absence of any observation studies or clinical trials in children, restriction of dietary oxalate is not generally recommended for children.
Foods that have shown to increase the amount of oxalate in urine include: spinach, rhubarb, nuts and wheat bran

Management of primary hyperoxaluria (PH):

- Treatment should be initiated with high fluid intake (2–3 l/m^2 per day), aiming at urine dilution by day and night, that may require tube feeding in young children but often fails due to non-compliance.
- Urinary pyrophosphate, citrate, and magnesium are inhibitors of calcium oxalate precipitation. Thus, the solubility of calcium oxalate may be increased by the administration of neutral phosphate (orthophosphate, in a dose of 30 to 40 mg/kg but higher during periods of skeletal growth, maximum dose 60 mg/kg per day), potassium citrate (0.15 g/kg), and/or magnesium oxide (500 mg/day per m^2).
- Restriction of dietary oxalate intake has limited influence on the disease.
- A trial of high-dose pyridoxine (pyridoxal phosphate), a coenzyme of AGT that promotes the conversion of glyoxylate to glycine, rather than to oxalate. About 30 to 50 percent of patients with PH type 1 will respond to pyridoxine therapy. Hence, a trial of pyridoxine that lasts at least three months is warranted in all patients with type 1 PH.

Cystinuria

- High fluid intake (2 L/m^2 per day) well distributed over day- and night-time
- Sodium restriction intake, because of competition transport of sodium against amino acids at the apical side of the tubular cell
- Urine alkalinization using orally administered potassium citrate
- Low protein diet in order to limit methionine (precursor of cystine)-rich food (eggs, fish, meat, cheese)
- Agents such as α-mercaptoproionylglycine (tiopronine, 20 mg/kg per day) or D-penicillamine (20 mg/kg per day) are capable of forming highly soluble mixed disulphides with cystine moieties, especially when cystine excretion is more than 3 mmol per day; such components are 50-times more soluble than cystine. Alpha- mercaptoproionylglycine appears better tolerated than D-pencillamine. Titration of dose to maintain free urine cystine below 100umol/mmol creatinine appears helpful.
- Captopril has been advocated but results have been inconclusive.
- The follow-up of these patients is based on urine volume (target urine specific gravity<1010), urine pH (target 7.5-8), free urine cystine concentration (target<1 mmol/l), renal ultrasonography and, sometimes, urinary sodium (in order to estimate sodium intake). Therefore, the treatment must be personalized, and the amount of drug required is dependent on body size.
Hyperuricosuria

- Uric acid decreases the solubility of calcium oxalate, and hyperuricosuria is an independent risk factor for calcium nephrolithiasis. Consequently treating hyperuricosuria is recommended to decrease the risk of recurrent calcium stones.
- Purine restriction is the first-line treatment for adults, with allopurinol, an inhibitor of xanthine oxidase, indicated for nonresponders with associated hyperuricemia. A high purine diet includes foods like red meats, especially organ meats, and legumes and is responsible for enhanced uric acid formation and excretion.
- Currently the optimal treatment for children with hyperuricosuria and a history of calcium oxalate stones is uncertain, as protein intake should not be restricted during childhood and there have not been any randomized controlled trials or high quality observational studies of alternative treatment strategies.
- Pure uric acid stones are rare in children but should be treated when found. The major risk factors for uric acid stones are low urine volume, hyperuricosuria and low urine pH. Hydration and urinary alkalinization are highly effective to prevent uric acid stone recurrence.
- To reduce uric acid production, allopurinol has been used in select circumstances (Lesch–Nyhan disease or tumor lysis syndrome).

10a. Role of Renal Dietitian

- Renal Dietitian can help to develop a personalized diet planning to lower the risk of recurrence of stones based on metabolic risk factor.
- A dietitian can also help overweight people plan meals to help them lose weight. Studies have shown that being overweight increases the risk of kidney stones, particularly uric acid stones. Diets that are low in carbohydrates have been shown to further increase the risk of uric acid stones and should be avoided.
- Studies have shown the Dietary Approaches to Stop Hypertension (DASH) diet can reduce the risk of kidney stones. The DASH diet is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein.
10b. Follow up

Due to high risk of recurrence of nephrolithiasis in children long-term follow-up with periodic reassessments is indicated. Evaluation of metabolic stone forming activity, as determined by growth in size of existing stones or formation of new stones over time, is important in monitoring the effectiveness of treatment. The frequency of renal imaging required will depend upon the type and number of stones and the severity of the metabolic abnormalities detected. In most circumstances and in the absence of symptoms or infection, once yearly or every other year imaging is sufficient. Patients with significant metabolic problems such as primary hyperoxaluria, cystinuria, marked hypercalciuria, and those with infected stones (which can develop and grow quickly) may require more frequent evaluations. Acute symptoms at any time should prompt reevaluation. If existing stones increase in size, or new stone formation occurs despite treatment, a more intensive regimen should be implemented. In children of all ages, if adherence with recommendations can be secured, response to treatment is typically excellent, with reduced frequency or elimination of active stone formation.
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Appendix:

Figure 1: Summary of the glyoxylate metabolism in human hepatocytes. Simplified pathways involving glycine, glycolate, and hydroxyproline as the main sources of glyoxylate. Peroxisomal glyoxylate is detoxified by alanine-glyoxylate aminotransferase (AGT), while mitochondrial and cytosolic glyoxylate is reduced to glycolate by glyoxylate reductase/hydroxypyruvate reductase (GRHPR), preventing excessive oxidation to oxalate by LDH. Hydroxyproline metabolism results in the production of 4-hydroxy-2-oxoglutarate that is normally split into glyoxylate and pyruvate by 4-hydroxy-2-oxoglutarate aldolase (HOGA1). PyrOHcarbox=pyrrolene-5-carboxylate; HGlu= 4-hydroxy-glutamate; HO-Glu=4-hydroxy-2-oxoglutarate.
Figure 2: Algorithm for hyperoxaluria diagnosis (used with permission from Dawn Milliner, MD Mayo Clinic, Dawn Milliner, MD, Mayo Clinic, Rochester Minnesota and V. O Edvardsson, MD, Landspitali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
**Figure 3:** Schematic overview of adenine metabolism. In adenine phosphoribosyltransferase deficiency, adenine cannot be converted to adenosine monophosphate and is instead converted by xanthine dehydrogenase to 2, 8-dihydroxyadenine. HPRT deficiency results in hyperuricemia. XDH deficiency results in Xanthinuria. Abbreviations: APRT, adenine phosphoribosyltransferase; AMP, adenosine monophosphate; HPRT, hypoxanthine-guanine phosphoribosyltransferase; IMP, inosine monophosphate; XDH, xanthine dehydrogenase

11 (with permission from V. O Edvardsson, MD, Landspitali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
**Figure 4:** Algorithm for APRT deficiency diagnosis\textsuperscript{11} (used with permission from Dawn Milliner, MD Mayo Clinic, Dawn Milliner, MD, Mayo Clinic, Rochester Minnesota and V. O Edvardsson, MD, Landspitali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
Figure 5: Algorithm for Cystinuria diagnosis\textsuperscript{11} (used with permission from Dawn Milliner, MD Mayo Clinic, Dawn Milliner, MD, Mayo Clinic, Rochester Minnesota and V. O Edvardsson, MD, Landspítali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
Figure 6: Algorithm for Dent Disease diagnosis (used with permission from Dawn Milliner, MD Mayo Clinic, Dawn Milliner, MD, Mayo Clinic, Rochester Minnesota and V. O Edvardsson, MD, Landspitali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
Figure 7: Algorithm for FHHNC diagnosis \(^{11}\) (used with permission from Dawn Milliner, MD Mayo Clinic, Dawn Milliner, MD, Mayo Clinic, Rochester Minnesota and V. O Edvardsson, MD, Landspítali University Hospital Hringbraut, Iceland; The Rare Kidney Stone Consortium)
Figure 8: *Acute Stone Emergency Center Protocol used at Texas Children’s Hospital*

**Acute Stone Pain Clinical Pathway**

- Suspected Stone
  - Obtain UA/Ucx, chem 7, CBC
  - Pain control: Toradol preferred
  - Start iv hydration

- Signs of septic shock
  - Yes: Resuscitate
    - Consider bedside U/S
    - Consult Urology
  - No:
    - Renal/bladder US
      - With any degree of hydronephrosis or hydroureters?
        - Yes:
          - Stone?
            - Yes: Disposition per EC
            - No: Noncontrast CT abd/pelvis
          - No: Stone on CT
            - No stone on CT: Disposition per EC
        - No: Adequate pain control, well hydrated and able to tolerate PO?
          - Yes: Disposition per EC
          - No:
            - Solitary kidney or fever and positive UA or +/- severe hydronephrosis
              - Yes: Consult urology
              - No: Discharge home with:
                1. Pain meds
                2. Flomax 0.2 mg QHS for children <4 and 0.4mg QHS for children ≥4 for 21 days
                3. Direct schedule with urology for 2 weeks
                4. Instruct pt to strain urine
                5. Use smart phrase in discharge instructions: _ECStone_