

**Update – 2022 Canadian Urological Association guideline: Evaluation and medical management of the kidney stone patient**

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**Introduction**

Despite advances in the surgical management of urinary stone disease that have significantly reduced patient morbidity, new stone formation and recurrence remain significant health issues. Data from the United States National Health and Nutrition Examination Survey (NHANES) published in 2020 reported a kidney stone prevalence of 12% in men and 10% among women.<sup>1</sup> Recent data from the US also has noted a cumulative increase in stone incidence from 0.6% to 0.9% between 2005 and 2015.<sup>2</sup> An increase in stone formation among women has also been observed such that the male to female ratio appears to be decreasing.<sup>3,4</sup> Evidence is also emerging there may be an increase in the incidence of certain stone compositions such as uric acid, a stone type linked to both dietary and metabolic risk factors.<sup>5</sup> Furthermore, the association with obesity, metabolic syndrome, diabetes mellitus and stone formation suggests nephrolithiasis should be regarded as a systemic disease.

Recurrence rates after an initial symptomatic stone event are reported to be 30-50% within 10 years.<sup>6,7</sup> Therefore, patients are generally motivated to explore prevention strategies.<sup>1</sup> 96.8% of recurrent stone formers or those with more than one concurrent stone will have a urinary metabolic abnormality.<sup>8</sup> Epidemiological data from the US show that only 7% of patients

with a high risk of recurrent stone disease undergo metabolic evaluation by any physician.<sup>9</sup> 81% of patients interviewed would prefer to take prophylactic medication than undergo another stone episode, and 92% of respondents preferred medication to undergoing surgery.<sup>10</sup> Although patients indicate they would be interested in using medication to prevent future stones, compliance studies suggest otherwise. Close to 50% of patients prescribed pharmacological prevention were non-compliant, especially those on potassium citrate.<sup>11</sup> This data stresses the importance of a comprehensive metabolic assessment with implementation of individualized prevention strategies. With directed therapy and proper patient education, patient compliance and therapeutic success may be optimized.

The economic burden of recurrent stone disease is also significant. Estimates of direct costs for patient care and the indirect costs related to lost work time exceed \$5 billion USD.<sup>12,13</sup> Given the rising rates of obesity and diabetes and their association with stone formation, the cost of managing stone disease is expected to increase to 1.24 billion dollars yearly in the US by 2030.<sup>14</sup>

This guideline is an update of the 2016 document and aims to identify patients at heightened risk of stone recurrence, to outline the required investigations to assess these patients, and to provide contemporary advice on dietary and medical interventions of proven benefit in the Canadian context. This current guideline addresses the evaluation and medical prophylaxis of upper urinary tract stones and not bladder stones.

### **Literature review**

The updated content included in this document is based on a review of the English language literature. A PubMed search was conducted encompassing the period from January 1, 2015 to July 1, 2021 to include the following terms: “nephrolithiasis”, “urolithiasis”, “kidney stone”, “renal stone”, or “urinary stone”. In total, 11,640 article titles were reviewed and 293 were identified as potentially relevant for inclusion in the literature assessment for this guideline update. Management recommendations were modified if needed based on the most current literature since the last guideline was published in 2016. Studies were evaluated and recommendations made based on Oxford levels of evidence and grades of recommendation as per the CUA Guidelines Committee’s directive.<sup>15</sup>

### **Indications for metabolic evaluation**

**Recommendation: Basic metabolic screening should include a urinalysis, with or without a urine culture, serum electrolytes (Na, K, HCO<sub>3</sub>), calcium, creatinine, and a stone analysis when available (LE 4, Grade C recommendation).**

A first time stone former, without any identifiable risk factors for recurrent stone formation, should undergo a limited metabolic screen to rule out potential systemic disorders such as hyperparathyroidism and renal dysfunction.

**Recommendation: An in-depth metabolic evaluation is recommended in patients with risk factors for recurrent stone disease (LE 3, Grade C recommendation).**

An in-depth metabolic investigation may be considered for *any* patient who is motivated and interested in completing metabolic testing. There are however, patient populations with clearly known risk factors where an in-depth metabolic investigation is recommended:<sup>16-23</sup>

- Children (<18 years of age)
- Bilateral or multiple stones
- Recurrent stones ( $\geq 2$  kidney stone episodes)
- Non-calcium stones (e.g. uric acid, cystine)
- Pure calcium phosphate stones
- Any complicated stone episode that resulted in a severe (if even temporary) acute kidney injury, sepsis, hospitalization, or complicated hospital admission
- Any stone requiring percutaneous nephrolithotomy treatment
- Stones in the setting of a solitary (anatomical or functional) kidney
- Patients with renal insufficiency
- History of systemic disease that increases the risk of kidney stones (e.g. gout, osteoporosis, inflammatory bowel disorders, hyperparathyroidism, renal tubular acidosis, sarcoidosis, diabetes mellitus/metabolic syndrome)
- Occupation where public safety is at risk (e.g. pilots, air traffic controller, police officer, military personnel, firemen)
- Family history of kidney stones

Struvite stones typically form in the setting of recurrent urinary infection, anatomical anomalies, and foreign bodies but occasionally are associated with metabolic abnormalities. Metabolic evaluation maybe considered in these patients although the prevention focus should be on addressing the risks mentioned with periodic imaging surveillance if risk factors are not modifiable. The urease inhibitor acetohydroxamic acid (AHA) has been used with limited success and with significant side effects.<sup>24-26</sup> This agent is not currently available in Canada.

### ***In-depth evaluation***

For those patients where an in-depth evaluation is indicated, the work-up should include serum and 24-hour urine tests as well as a thorough dietary history. These tests should include:

#### ***Serum:***

- Creatinine, sodium, potassium, calcium, albumin, uric acid, and bicarbonate.

- Parathyroid hormone (PTH) level if high or high-normal serum calcium, or if idiopathic hypercalciuria with normocalcemia.
- Vitamin D level if PTH is elevated to rule out secondary hyperparathyroidism

*24-hour urine collection:*

- Volume, creatinine, calcium, sodium, potassium, oxalate, citrate, uric acid, magnesium
- Cystine if known or suspected cystine stone

*Spot urine:*

- Urinalysis with urine pH

Previously, it was suggested that PTH testing was only required if serum calcium was elevated.<sup>27</sup> However, more recent data suggests that normocalcemic hyperparathyroidism is an important clinical variant that is associated with a high prevalence of nephrolithiasis.<sup>28</sup> Screening for primary hyperparathyroidism in a tertiary stone clinic demonstrated a prevalence of 7.1% with 71.7% of those cases having high-normal serum calcium.<sup>29</sup> Therefore, we recommend serum PTH if the patient has a high or high-normal serum calcium or in patients with idiopathic hypercalciuria and normocalcemia.

Vitamin D deficiency is common in North American populations and new and evolving data has emerged regarding the impact of vitamin D on stone disease (see Vitamin D section below). Based on this evidence, we recommend that serum vitamin D be measured (if available in your health region) when a patient has an elevated PTH in order to rule out secondary hyperparathyroidism.

### **Number of 24-hour urine collections**

**Recommendation: Two 24-hour urine collections are preferred when possible but should be balanced by the practicality and importance of obtaining at least one collection (LE 3, Grade C recommendation).**

There is some controversy regarding the number of 24-hour urine collections that are necessary in order to investigate patients.<sup>30,31</sup> Data suggests that 47.6% of patients had their clinical management changed by an abnormality identified only when two samples were collected.<sup>32,33</sup> Close to 25% of patients will have a 50% variation in at least one urinary parameter, and 25% of patients will have a 20% difference in three urine parameters.<sup>34</sup> As such it is currently recommended that two 24-hour urine collections be obtained. The benefit of two collections should be balanced however, by the practicality and importance of obtaining at least one collection.

## Importance of stone analysis

**Recommendation: Stones collected by patients or removed at the time of surgical intervention should be submitted for analysis (LE 3, Grade C recommendation).**

Identification of stone composition will aid in determining prevention and directing surgical options for future stones. Furthermore, identification of struvite, ammonium urate, uric acid, calcium phosphate, or cystine stones would alter the indication for in-depth metabolic evaluation. If a patient continues to form new stones, a repeat stone analysis should be performed as this may change management. Stone composition changed in 21.2% of patients over time.<sup>35</sup>

Reports have demonstrated a strong correlation between pure stone composition and metabolic abnormalities.<sup>36</sup> Specifically, hypercalciuria was associated with brushite and calcium oxalate dihydrate stones; whereas, hyperoxaluria was found most commonly in calcium oxalate monohydrate stone formers.<sup>37</sup> In addition, apatite stones were correlated with both hypercalciuria and hypocitraturia, and uric acid stones were found in patients with low urinary pH.<sup>36</sup> Stone composition may be a useful tool to help guide empiric medical therapy for patients who are unable or unwilling to perform an in-depth medical evaluation.<sup>37</sup>

## General dietary measures

**Recommendation: When possible specific dietary assessments and recommendations should be made with the involvement of a registered dietician (LE 3, Grade C recommendation).**

General dietary and fluid intake advice has been shown to be effective in reducing stone recurrence rates and is warranted for even the first-time stone former without identifiable risk factors. The “stone clinic effect” has shown that counseling on appropriate fluid intake and dietary excesses can significantly reduce stone recurrence.<sup>38</sup>

The involvement of a registered dietician, if available, in the counseling of patients with recurrent renal stones should be incorporated into the management of these patients. Assessment with a registered dietician is strongly suggested where there is a history of compromised nutritional status, complex medical situations, or patients who need assistance implementing dietary recommendations.<sup>39,40</sup> Evidence suggests that patients who received specific dietary recommendations based on a comprehensive evaluation had fewer stone recurrences over 3 years than those who only received general dietary advice.<sup>41</sup>

## Fluid intake

**Recommendation: All stone formers should be counseled to achieve a daily urine output of 2.5 liters (LE 2, Grade B Recommendation).**

Adequate fluid intake to produce a urine output of 2.5L daily has been shown to reduce the risk of stone formation by 60-80% in several meta-analyses.<sup>42-46</sup> Conversely, studies have shown that poor fluid intake increases lithogenic risk particularly with 1.4L of urine or less.<sup>45,47-49</sup> Adequate fluid intake in the form of water is suggested as the first line treatment to prevent stones with each 200mL increase in fluid intake reducing the risk of stones by 13%.<sup>50</sup>

Other fluids, including orange juice, caffeinated beverages (or caffeine alone), coffee, wine and beer may have a protective effect against stone formation which must be weighed against other potential health effects.<sup>51-54</sup> The consumption of low-calorie orange juice has been shown to have a protective effect by increasing urinary citrate levels.<sup>55</sup> Additionally, sugar sweetened non-colas and colas may increase the risk of stone formation.<sup>52</sup> Milk does not increase the risk of stones unless consumed in excess. Lastly no conclusive evidence exists regarding the specific properties of water (e.g. water hardness) and lithogenic risk.<sup>48</sup>

Recent studies assessing smart technology including smart water bottles and associated digital applications have shown the accuracy of these technologies to measure fluid intake, however the impact on urine output may be similar to counseling.<sup>56-58</sup> A systematic review showed that most interventions can improve fluid intake by approximately 500mL, with the most effective strategies being instruction, and self-monitoring using urine dipstick or 24-hour urine volume.<sup>59</sup>

Counseling regarding fluid intake should clearly state the risk reduction associated with increased fluid intake, explore barriers to fluid consumption such as occupational barriers, taste factors related to water, and urinary voiding difficulties such as overactive bladder and bladder outlet obstruction.<sup>60,61</sup> Practical ways to increase fluid intake include drinking at set times during the day and hourly during working hours, maintaining a water bottle in all places where significant time is spent, and eating foods higher in water content such as fruits and vegetables.<sup>61</sup> Caution should be exercised when counselling patients with congestive heart failure or chronic renal insufficiency.

## Calcium

**Recommendation: The goal for dietary calcium intake should be 1000-1200mg/day and if calcium supplementation is required it should be taken at mealtimes (LE 3, Grade B Recommendation).**

A public misconception persists that stone formers should restrict calcium in their diet. On the contrary, multiple large, prospective cohort studies have demonstrated higher dietary intakes of calcium are correlated with a lower risk of stone formation in both men and women.<sup>46,62-64</sup> Previous studies examining the effect of calcium supplementation on stone risk have shown conflicting results; with one study demonstrating a slightly increased risk in stone formation<sup>63</sup>, and another study showing no change in risk.<sup>47</sup> The difference in these findings may

be attributed to the timing of the calcium supplement administration, since calcium not consumed at mealtimes in one study may have decreased its ability to chelate oxalate.<sup>64</sup>

The recommended daily intake of calcium is 1000–1200mg separated into 2 doses and ideally with meals. Calcium would preferably be obtained through diet as some studies suggest supplementation may also increase cardiovascular risk.<sup>65</sup> Where supplementation is required it should be taken with meals as this results in the greatest oxalate sequestration and is not associated with an increased risk of hypercalciuria.<sup>65</sup>

### Vitamin D and bone health

#### Recommendations:

1. **In calcium stone formers with vitamin D deficiency, repletion is appropriate however, monitoring of vitamin D levels and hypercalciuria on repeat testing is necessary** (*LE 2-3, Grade C Recommendation*).
2. **Consider bone mineral density testing in calcium stone formers with evidence of hypercalciuria and/or distal renal tubular acidosis (dRTA)** (*LE 2-3, Grade C Recommendation*).
3. **Treatment of calcium stone formers with either a thiazide diuretic, alkali citrate or ideally both has been shown to reduce stone recurrence risk and increase bone mineral density and should be considered in patients with documented low bone mineral density** (*LE 2-3, Grade C Recommendation*).

Vitamin D deficiency is common among stone formers in northern latitudes, with 80.2% of patients in a Canadian metabolic stone clinic having vitamin D insufficiency.<sup>66-68</sup> Patients with low vitamin D levels have been shown to have an increased number of metabolic abnormalities; specifically, secondary hyperparathyroidism which was found in 26% of a Canadian cohort.<sup>67</sup> Studies examining serum vitamin D levels and urinary calcium excretion are conflicting. Some studies noted an association between higher vitamin D levels and hypercalciuria,<sup>66,69</sup> whereas others have failed to find a relationship between vitamin D and hypercalciuria,<sup>70</sup> or stone re-occurrence.<sup>71</sup>

The impact of vitamin D supplementation on hypercalciuria and stone risk is unclear. The largest study to date examining the effect of vitamin D in the general population evaluated over 200,000 men and women found no association between vitamin D intake and urolithiasis.<sup>72</sup> Similarly, a meta-analysis of 10 randomized controlled trials of vitamin D supplementation including 2,010 participants showed no increased incidence of kidney stones.<sup>73</sup> Several other large studies have shown an increased risk of stone formation with vitamin D supplementation; however, these studies were confounded by the co-administration of calcium supplementation.<sup>74-</sup>

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Previous studies in stone formers with vitamin D deficiency have found mixed effects of vitamin D repletion on urinary calcium excretion. Two prospective cohort studies of vitamin D supplementation in patients with vitamin D deficiency did not show an increase in mean calcium excretion.<sup>66,77</sup> A recent randomized trial showed no effect of vitamin D administration on urinary calcium excretion or the supersaturation of calcium oxalate or calcium phosphate crystals.<sup>78</sup>

Although we do not recommend routinely testing vitamin D levels (see metabolic evaluation above), chronic depletion of vitamin D may lead to secondary hyperparathyroidism thereby increasing the risk of bone loss and recurrent stones. Consequently, vitamin D levels should be measured in the settings of an elevated PTH level in order to rule out secondary hyperparathyroidism. Repletion of vitamin D in stone formers is appropriate with follow-up monitoring for vitamin D response and the development of hypercalciuria.

The association between low bone mineral density (BMD) and calcium nephrolithiasis has been well investigated. Several studies have demonstrated that calcium stone disease correlates with low BMD, with a higher risk corresponding with increasing levels of hypercalciuria.<sup>79-82</sup> Furthermore, the prevalence of osteopenia or osteoporosis is higher in stone formers with concomitant vitamin D deficiency.<sup>80</sup> Chronic metabolic acidosis in patients with complete distal renal tubular acidosis (dRTA) increases bone resorption and places these patients at very high risk of low BMD; one series demonstrated rates of osteopenia and osteoporosis as high as 43% and 21% respectively.<sup>83</sup> Multiple studies have shown an increased risk of fractures in patients with urolithiasis (HR 1.13-2.32).<sup>84,85</sup>

Dietary recommendations for stone reduction including a low sodium and normal calcium diet have also been shown to improve BMD.<sup>86</sup> Thiazide diuretics also reduce urinary calcium levels, decrease stone recurrence,<sup>867</sup> improve BMD in stone formers<sup>85,87,88</sup> and reduce the risk of hip fractures.<sup>89</sup> In addition, alkali citrate therapy has a positive effect on both stone recurrence and bone health by reducing bone resorption and buffering acid production. Treatment with potassium citrate monotherapy effectively increases BMD in calcium stone formers and is effective in patients with dRTA.<sup>87,90,91</sup> Several studies have examined combination therapy with both thiazides and potassium citrate and found significant improvements in both BMD and stone recurrence.<sup>87,92</sup> While more prospective studies are required, combination therapy may be more effective than either monotherapy. Bisphosphate therapy has also been shown to be safe and effective in increasing BMD in patients with urinary stones.<sup>86</sup>

### **Animal protein**

**Recommendation: Patients with recurrent calcium or uric acid stones should moderate their animal protein intake and avoid purine rich foods (LE 2-3, Grade C Recommendation).**

In some populations, high animal protein is associated with a slight increase in the risk of nephrolithiasis.<sup>63</sup> A large, prospective cohort study of men showed that dietary protein consumption was directly associated with the risk of stone formation (RR 1.33).<sup>62</sup> Similarly, idiopathic calcium stone formers have been noted to have an increased consumption of protein (animal and vegetable) and purine rich foods compared to non-stone formers, resulting in elevated urinary oxalate and calcium, and lower levels of urinary citrate.<sup>93</sup>

However, other studies have failed to find a strong correlation between animal protein intake and the risk of nephrolithiasis.<sup>47,48,94</sup> Regardless, diets high in animal protein are associated with increased uric acid excretion, decreased urinary citrate and pH levels predisposing these individuals to uric acid nephrolithiasis.<sup>95</sup> A vegetarian diet has been demonstrated to reduce the risk of uric acid crystallization by 93% compared to a typical Western diet.<sup>96</sup>

## Sodium

**Recommendation: Patients with recurrent calcium nephrolithiasis should limit their sodium intake to 1500mg daily and not exceed 2300mg daily (*LE 1-2, Grade B Recommendation*).**

Dietary sodium excess is associated with hypercalciuria,<sup>97</sup> and high urinary sodium levels increase calcium excretion and decrease urinary citrate.<sup>35,38</sup> High sodium intake was associated with up to 61% increase in stone risk in a large prospective cohort of women.<sup>47</sup> Furthermore, reduction in dietary sodium can improve urinary parameters and decrease stone recurrence. In a randomized trial of hypercalciuric calcium stone formers, a low sodium diet resulted in lower urinary sodium, calcium, and oxalate; and resulted in normalization of urine calcium excretion for one third of patients.<sup>98</sup> An additional randomized trial demonstrated that a low sodium and animal protein diet resulted in fewer stone recurrences compared with a low calcium diet.<sup>99</sup>

## Fruits and vegetables

**Recommendation: A diet high in fiber, fruits, and vegetables may offer a small protective effect against stone formation (*LE 2-3, Grade C Recommendation*).**

Low dietary intake of fiber, fruit, and vegetables increases the risk of kidney stones in women.<sup>100</sup> In stone forming patients with hypocitraturia, introducing these foods resulted in increased excretion of citrate, potassium, and magnesium and a reduction in the supersaturation of calcium oxalate and calcium phosphate crystals.<sup>101</sup>

## Vitamin C

**Recommendation:** Vitamin C supplementation of more than 1000mg daily is not recommended due to the associated risk of hyperoxaluria and nephrolithiasis (LE 2-3, Grade C Recommendation).

It is theorized that the excess vitamin C is converted to oxalate and may increase stone risk. In population-based studies intake of over 1000mg of vitamin C daily caused a slight increase in the risk of nephrolithiasis.<sup>63</sup> Vitamin C supplementation of 1 to 2g was associated with increased urinary oxalate in stone forming patients.<sup>102,103</sup>

## Metabolic syndrome

**Recommendation:** Stone disease highly correlates with obesity, diabetes, and metabolic syndrome; and patients should be counselled that proper management of these conditions may reduce their future stone risk (LE 2-3, Grade D Recommendation).

Patients with one or more features of metabolic syndrome have significantly increased risks of heart disease, myocardial infarction, angina, and coronary bypass.<sup>104</sup> Stone disease is also linked to metabolic syndrome, where patients with metabolic syndrome have a 2.13 times increased odds of developing stones.<sup>105</sup> In addition, the risk of stone disease increases with the number of metabolic syndrome traits present.<sup>105</sup>

Patients with metabolic syndrome and stones should be counselled to adopt healthier lifestyles, including dietary practices that promote low sodium intake and consumption of fresh fruit and vegetables. The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to be effective in reducing cardiovascular risks as well kidney stone recurrence in three large epidemiological studies.<sup>106</sup>

Obesity and diabetes have been shown to be independent risk factors for stone formation, likely secondary to the development of acidic urine promoting uric acid crystal formation.<sup>107-110</sup> The underlying insulin-resistance in these patients leads to impaired glutamine metabolism, ammonia production, and ammonium excretion. This results in unbuffered hydrogen ions and a lowering of the urinary pH.<sup>111</sup> Recent evidence suggests pioglitazone, a thiazolidinedione used in the treatment of type 2 diabetes can reduce insulin-resistance leading to increases in ammonium excretion and more alkaline urinary pH values, which may be protective against stone disease.<sup>112</sup>

## Oxalate

### Recommendations:

1. **Patients with hyperoxaluria should minimize their intake of high-oxalate foods. Vitamin B6 supplementation can be considered to lower urinary oxalate levels, when dietary modification has been unsuccessful (LE 2-3, Grade C Recommendation).**
2. **In patients with enteric hyperoxaluria, elemental calcium or calcium citrate should be given with meals to bind with dietary oxalate to reduce its intestinal absorption (LE 2-3, Grade C Recommendation).**

Hyperoxaluria can result from dietary, enteric, or idiopathic causes and is associated with an increased risk of calcium oxalate stone formation.<sup>113</sup> Treatment of dietary and idiopathic hyperoxaluria with a low oxalate diet has shown mixed results. Most studies have demonstrated that a low oxalate diet reduces urinary oxalate levels; however, this did not consistently result in a decrease in calcium oxalate crystal supersaturation.<sup>114,115</sup> Multiple studies, including several prospective cohort studies and a randomized controlled trial have shown that vitamin B6 or pyridoxine supplementation (25mg daily) is effective in reducing urinary oxalate levels.<sup>116</sup>

Enteric hyperoxaluria, is due primarily to the malabsorption of intestinal fats in the ileum. This condition is most frequently found in patients with inflammatory bowel disease with small bowel involvement, short gut syndrome, and after bariatric surgery (not including restrictive bariatric procedures such as vertical banded gastroplasty and sleeve gastrectomy).<sup>117</sup> The intestinal fatty acids that are not absorbed cause saponification of calcium and magnesium in the intestinal lumen leading to a decreased amount of calcium available to bind dietary oxalate.<sup>117</sup> This results in increased availability and absorption of oxalate and hyperoxaluria. As these conditions are often associated with diarrhea, typical laboratory findings include low urine volume and pH, hypocitraturia, hypocalciuria (unique to malabsorptive disease) and hyperoxaluria.<sup>117</sup> Treatment includes reduction of dietary oxalate, increased fluid intake and calcium consumption.<sup>118</sup> The calcium can be elemental calcium or calcium citrate as this will help correct the hypocitraturia and low urinary pH as well. Importantly the calcium should be taken with meals for it to bind to the dietary oxalate.<sup>118</sup>

### Pediatric stone disease

**Recommendation: All children with stone disease should undergo an in-depth medical evaluation and may benefit from a multidisciplinary approach with Urology and Nephrology (LE 3, Grade D Recommendation).**

While pediatric stone disease is uncommon, with 59.5 cases per 100,000 person-years in the United States,<sup>119</sup> the incidence is increasing in many developed countries.<sup>120</sup> The recurrence rate is high, with 50% of patients forming a recurrent stone within three years of the index

stone.<sup>121</sup> Dietary factors, such as sodium and purine intake, low urine volume and climate are thought to play a role in increased stone risk. Obesity may not have the same effect on stone risk in children, as it does in adults.<sup>122-124</sup> Prematurity, medications (e.g. loop diuretics) and genetic factors also increase the risk of pediatric stone disease.

An in-depth metabolic evaluation has historically been recommended in all children. In toilet-trained children, an in-depth evaluation with a 24-hour urine collection is recommended by most experts. In non-toilet-trained children or when a 24-hour urine collection is not possible in a toilet-trained child, a spot or random urine collection may suffice. This would include a urinalysis, and spot urine calcium, oxalate, citrate, cystine, protein and uric acid.<sup>125</sup> The utility of a full metabolic stone evaluation has been called into question for first-time stone formers, as it changes management in only 11% of patients.<sup>126</sup>

In a population-based US study, metabolic abnormalities in children were as follows: hypercalciuria (62%), hyperoxaluria (18%), hypocitraturia (12%) with hyperuricosuria relatively rare compared to adults (9%).<sup>120</sup> Low urine volume may be affected by poor intake, access to clean drinking water, diarrhea, and other gastrointestinal illnesses. Recommended fluid intake is 70-100 ml/kg/day.<sup>127</sup>

Hypercalciuria is the most common metabolic abnormality and is often idiopathic. Management includes increasing fluid intake, reducing sodium intake and thiazide diuretics, if refractory. Hypocitraturia can be idiopathic or associated with other metabolic conditions (e.g. dRTA, high meat protein diet).<sup>128</sup> Hyperoxaluria can be primary (increased endogenous production), dietary or enteric.<sup>128</sup> Hyperuricosuria is relatively uncommon, as are uric acid stones. Most children with urinary stones will benefit from a multidisciplinary approach with Urology and Nephrology involvement.<sup>129</sup>

### **Specific prophylaxis based on stone composition**

In the following section, “index patients” have been created based on the predominant stone composition. Potential metabolic abnormalities will be described, and specific diet and medical interventions will be highlighted for each clinical scenario.

#### ***Index Patient 1: Calcium oxalate or mixed calcium oxalate/calcium phosphate stones***

##### **Recommendations:**

- 1. Thiazide diuretics decrease urinary calcium and stone recurrence in calcium stone forming patients. (LE 1-3, Grade A-B Recommendation).**
- 2. Alkali citrates are effective in increasing urinary citrate and reducing stone recurrence in calcium stone formers (Level of Evidence 1-3, Grade A-B Recommendation).**

- 3. In calcium stone formers allopurinol is effective in reducing stone recurrence in patients with hyperuricemia but does not provide any benefit in patients with normal serum uric acid levels (LE 1-2, Grade B Recommendation).**
- 4. Empiric treatment with either thiazide diuretics and/or alkali citrates reduces stone recurrence in calcium stone formers with active stone disease who have normal metabolic evaluations (LE 1-3, Grade B Recommendation).**

Patients with calcium oxalate or combined calcium oxalate/calcium phosphate stones may have normal 24-hour urine testing, hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, low urine volume, or a combination of any of these features.<sup>130</sup> Based on 24-hour urine results various interventions can be considered (Figure 1).

Elevated urinary sodium can result in hypercalciuria and should be corrected through dietary reduction of sodium intake prior to initiating thiazide therapy.<sup>31,34,96</sup> In patients with recurrent calcium stones with and without metabolic abnormalities thiazide use decreases urinary calcium and stone recurrence.<sup>131-138</sup>

Dosages used in clinical trials are hydrochlorothiazide (25mg orally, twice daily or 50mg orally, once daily), chlorthalidone (25mg orally, once daily can be increased to 50mg), and indapamide (1.25mg orally, once daily can be increased to 2.5mg). The dose-dependent side effects of thiazide diuretics include hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypomagnesemia, and hypocitraturia. Combining thiazide diuretics with potassium citrate or potassium chloride prevents hypokalemia and hypochloremic metabolic alkalosis which can lead to hypocitraturia.<sup>139,140</sup>

Alkali citrate (potassium citrate, potassium magnesium citrate, sodium citrate) have been evaluated in several studies for the prevention of calcium nephrolithiasis. Alkali citrate increases urinary citrate levels and decreases the risk of recurrent nephrolithiasis.<sup>141-149</sup> Potassium citrate is the most studied agent with dosages in clinical trials ranging from 30-60mEq in two to three divided doses daily. Gastrointestinal upset is the primary side effect. Overall, potassium citrate is preferred over sodium citrate as the sodium load may increase urinary calcium excretion.<sup>150</sup>

Studies regarding hyperuricosuria in calcium oxalate stone disease show mixed results. In a large cross-sectional study, elevated urinary uric acid levels were not associated with calcium oxalate stone formation.<sup>151</sup> However, multiple studies have demonstrated treating hyperuricosuria in calcium oxalate stone formers reduces stone recurrence.<sup>152-154</sup> Hyperuricemia may be treated with a xanthine oxidase inhibitor, most frequently allopurinol at a dose of 200-300 mg daily. Major side effects include rash, gastrointestinal upset, abnormal liver enzyme levels, and prolonged elimination in renal disease.

Empiric preventative treatment with a thiazide diuretic and or alkali citrate can be considered in calcium stone formers with a normal metabolic workup who continue to have active stone disease. Randomized controlled trials in calcium stone formers have demonstrated

that thiazide diuretics were effective in reducing stone recurrence compared to placebo even in patients with normocalciuria.<sup>132,138</sup> Similarly, a prospective double-blind study demonstrated decreased stone events in calcium stone patients without hypocitraturia treated with potassium-magnesium citrate.<sup>146</sup>

### ***Index Patient 2: Pure calcium phosphate stones***

**Recommendation: Patients with incomplete or complete distal renal tubular acidosis (dRTA) should be treated with alkali citrate therapy (LE 2-3, Grade C Recommendation).**

Patients who form pure calcium phosphate stones may have an underlying condition such as dRTA or primary hyperparathyroidism. Suggestive biochemical features and treatment of these disorders are listed in Table 1.

Patients with primary hyperparathyroidism have a significantly increased risk of renal stone disease.<sup>155,156</sup> Even in patients with normal serum calcium levels an elevated PTH can increase stone risk, and result in decreased BMD.<sup>157,158</sup> Surgery for primary hyperparathyroidism results in decreased serum calcium, stone formation, and an improvement in BMD.<sup>159</sup>

Patients with dRTA may present with recurrent calcium phosphate stones, nephrocalcinosis, systemic acidosis, osteoporosis, failure to thrive, or sensorineural hearing loss.<sup>160</sup> Patients with dRTA generally have severe hypocitraturia and are best treated with an alkali citrate.<sup>161,162</sup> In patients with dRTA treatment with potassium citrate resulted in correction of systemic acidosis, improvement in urinary parameters, reduced stone formation, and increased BMD.<sup>163</sup> Potassium citrate has demonstrated superior effects on urinary indices as compared to sodium citrate in patients with dRTA.<sup>150</sup>

Incomplete dRTA is a condition characterized by defective urinary acidification similar to complete dRTA, without systemic metabolic acidosis.<sup>164</sup> Patients with incomplete dRTA still have disturbed calcium, citrate and bone metabolism resulting in recurrent stone formation and increased bone turnover.<sup>165</sup> Incomplete dRTA is likely a significantly underrecognized clinical condition due to the lack of a clear consensus on diagnostic criteria; however, the prevalence has been found to be as high as 15% in stone formers.<sup>166,167</sup> Incomplete dRTA should be suspected in patients with persistently alkaline urine (pH>5.3), low urinary citrate, and low-normal serum potassium and bicarbonate levels.<sup>164,167</sup> Similar to complete dRTA, the mainstay of treatment is alkali citrate therapy which improves urinary citrate and reduces stone formation.<sup>162</sup>

*Index Patient 3: Uric acid stones*

**Recommendation: In patients with uric acid stones, urinary alkalization to a pH of 6.5 is first-line therapy. Allopurinol may be used as adjunctive therapy in patients with hyperuricemia or hyperuricosuria (LE 1-3, Grade B Recommendation).**

Uric acid stone formers are at significant risk of recurrence. Uric acid stones may form as the result of several underlying disorders including obesity, diabetes mellitus, gout, excessive bicarbonate loss due to high output bowel disease, myeloproliferative disorders, and tumor lysis syndrome.<sup>5,168</sup> Uric acid stone formation is most associated with low urinary pH and low urine volume rather than hyperuricosuria.<sup>151</sup> The focus of prevention therefore, should be to correct urine pH above 5.5 and increase urine volume (Figure 2).<sup>168</sup> Xanthine oxidase inhibitors such as allopurinol or febuxostat can be used as adjunctive therapy in patients with demonstrated hyperuricemia, hyperuricosuria, or a history of gout after correction of urinary pH.<sup>169</sup>

Success with *in situ* uric acid stone dissolution has been demonstrated with alkali citrate, and maybe an underutilized treatment strategy.<sup>170,171</sup> In a recent prospective study, potassium citrate therapy was successful in dissolving 83% of stones (mean 1.4cm<sup>3</sup>) after 6 months of treatment.<sup>172</sup>

*Index Patient 4: Cystine stones*

**Recommendation: Cystine stone formers should be counselled to target 3L of urine output daily, restrict their sodium intake, and moderate their protein intake to reduce stone formation. Urinary alkalization of the urine targeting a urine pH of 7-7.5 is the initial therapy. Thiol-binding agents should be considered second line therapy (LE 3-4, Grade C Recommendation).**

Cystinuria, caused by a deficiency in reabsorbing dibasic amino acids, is a common genetic disorder affecting 1/7000 individuals. Cystine stone formers often present in childhood or as teenagers and maybe plagued by recurrent stone formation and the need for repetitive surgical intervention especially if prophylaxis is not optimized.

Patients with cystinuria should be encouraged to maintain a urine output of at least 3L daily (often demanding oral intake of 3.5–4L of fluid). This is a critical component of prevention in these patients as even with adjunctive medical therapy the success of stone prevention will be poor in patients who do not comply with increased fluid intake.<sup>173,174</sup> Sodium restriction is advised for all patients with cystinuria.<sup>174</sup> In small studies sodium restriction significantly decreased cystine excretion,<sup>175-177</sup> reflecting the coupling of cystine to parallel sodium transport in the kidney. Elevated dietary protein is associated with increased urinary cystine and a reduction in overall protein intake can decrease urinary cystine levels.<sup>178</sup>

The solubility of cystine increases significantly between urine pH of 7.0-7.5. Urinary alkalinization is therefore, the initial step in medical therapy with the goal of achieving a urine pH of greater than 7.0.<sup>179</sup> A urinary pH of greater than 7.5 should be avoided as this may promote calcium phosphate stone formation. Acetazolamide may be used as an adjunct to urinary alkalinization when potassium citrate alone is ineffective.<sup>180</sup> If alkalinizing agents fail to adequately control cystine stone formation thiol binding agents such as penicillamine 1-2g or tiopronin 800-1200mg in daily divided doses may be used.<sup>173,181-184</sup> Side effects from penicillamine can be significant and include fever, arthralgias, rash, dysgeusia, leukopenia, and proteinuria. Where available, tiopronin, should be prioritized due to its better side effect profile (asthenia, GI distress, rash, joint aches, and mental status changes) compared to penicillamine.<sup>182</sup> A small study evaluated the role of captopril however, significant reduction in stone formation was not achieved and captopril is no longer recommended.<sup>183</sup> Dietary and medical prevention options are shown in Figure 3.

Long-term compliance in patients with cystinuria can be difficult to achieve<sup>185</sup> and consideration should be given to management of these patients at specialized multidisciplinary clinics with close follow up.

#### **Future directions: Genetic screening in recurrent nephrolithiasis**

While not widely available, the genetic screening of patients with recurrent stone disease may have an increasing future role. It is likely that in addition to dietary and lifestyle choices, genetic factors are associated with recurrent nephrolithiasis. 35-65% of kidney stone patients have a family history of nephrolithiasis.<sup>186,187</sup> Heritability of kidney stones and urinary calcium excretion have been found to be greater than 45% in twin studies.<sup>188,189</sup> Underlying genetic causes are likely under-diagnosed, even in specialized renal stone clinics. In a study of nephrolithiasis and nephrocalcinosis patients recruited from renal stone clinics, 14.9% were found to have monogenic causative mutations, and 40% were novel.<sup>190</sup>

There have been more than 30 identified kidney stone genes representing different mechanisms leading to stone disease.<sup>191</sup> These mutations represent renal tubular disorders, abnormal calcium and vitamin D metabolism, and other inborn errors of metabolism. Cystinuria is the most common of these genetic causes.<sup>190</sup>

Diagnosing genetic disorders may lead to targeted prevention and provide an opportunity for genetic counselling. Lumasiran, a novel RNAi therapy for primary hyperoxaluria type I, has been developed, shown promising results in phase 3 trials, and was recently approved by Health Canada.<sup>192</sup> A multidisciplinary team approach including urologists, nephrologists, endocrinologists, and clinical geneticists can help coordinate biochemical and genetic testing and facilitate selection of optimal treatment strategies.<sup>193</sup>

### Summary

For patients at risk of recurrent renal stones, a detailed medical evaluation and an individualized approach to dietary and pharmacological prevention are important aspects of their care. The frequency of follow up and the need for repeat metabolic testing is not clearly defined in the literature and must therefore also be individualized. In patients where specific medical prophylaxis has been prescribed, re-evaluations with repeat metabolic testing within 6 months and yearly thereafter to monitor treatment efficacy and side effects are recommended.<sup>17</sup> Periodic imaging is also recommended for those harboring small asymptomatic stones.

Urologists, in addition to providing state-of-the-art surgical care to our patients should be capable of providing up-to-date metabolic assessment and optimal prevention strategies as part of a comprehensive approach to stone management.

DRAFT

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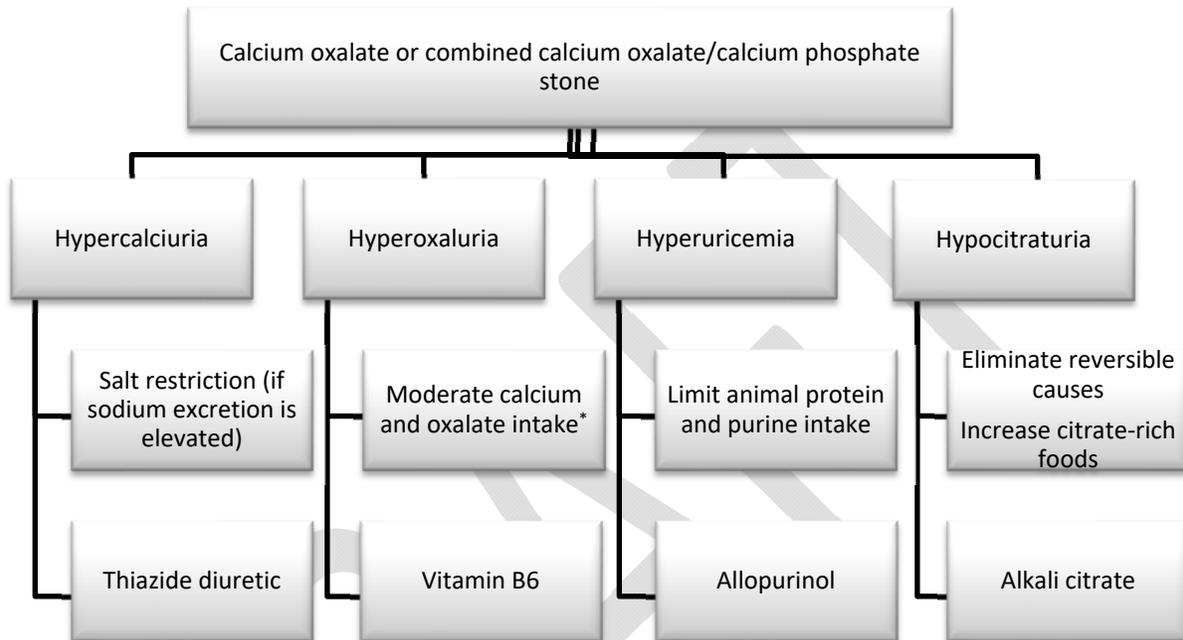
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DRAFT

## Figures and Tables

**Figure 1.** Specific dietary and medical treatments for patients with calcium oxalate or mixed calcium oxalate/calcium phosphate stones.



\*Calcium intake 1200 mg daily (with meals), moderation of foods high in oxalate, pair oxalate and calcium containing foods.

Figure 2. Specific dietary and medical treatments for patients with uric acid stones.

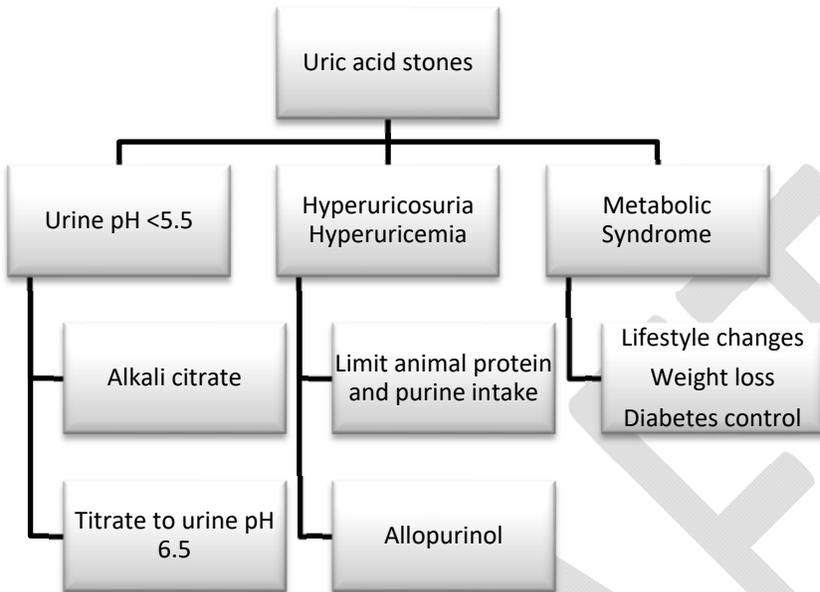
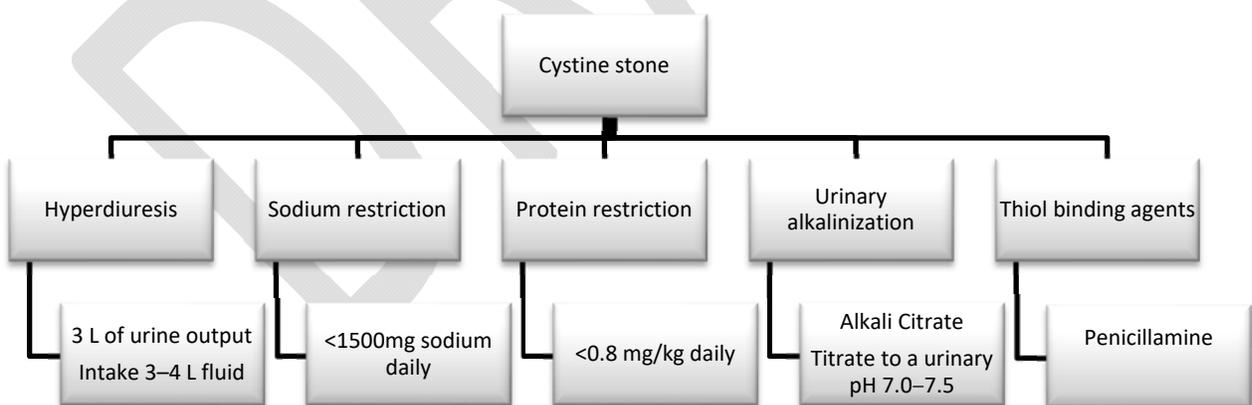


Figure 3. Specific dietary and medical treatments for patients with cystine stones



<b>Table 1. Characteristic findings, investigations, and treatment of primary/secondary hyperparathyroidism and distal renal tubular acidosis</b>			
<b>Disorder</b>	<b>Suggestive features</b>	<b>Investigations</b>	<b>Treatment</b>
Primary hyperparathyroidism	↑ or ↑N serum calcium ↑ or ↑N serum PTH Hypercalciuria Calcium oxalate or calcium phosphate stone ↓ Bone mineral density	Serum calcium  PTH  Vitamin D	Treat vitamin D deficiency  Referral to endocrinology
Secondary hyperparathyroidism	↑ serum PTH ↓ Vitamin D ↓ or N serum calcium Hypercalciuria ↓ Bone mineral density	Serum calcium  PTH  Vitamin D	Treat vitamin D deficiency  Consider referral to endocrinology
Complete distal renal tubular acidosis	Urine pH >5.8 ↓ serum bicarbonate ↓ serum potassium Pure apatite stone Hypocitraturia Hypercalciuria ↓ Bone mineral density	Serum electrolytes  Urine pH  24H Urine Collection	Alkali citrate  Thiazide
Incomplete distal renal tubular acidosis	Urine pH >5.3 ↓N serum bicarbonate ↓N serum potassium Pure apatite stone Hypocitraturia Hypercalciuria	Serum electrolytes  Urine pH  24H Urine Collection	Alkali citrate  Thiazide

PTH: parathyroid hormone, ↑ = high, ↑N = at the high end of normal range; ↓ = low, ↓N = at the low end of normal range.