

# Cystinuria: An Overview of Diagnosis and Medical Management

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## ABSTRACT

Cystinuria is a genetic disorder that causes recurrent nephrolithiasis. It is the most common type of monogenic stone disease accounting for 6%–8% of pediatric nephrolithiasis. Due to recurrent episodes of nephrolithiasis, it is associated with a very high prevalence of chronic kidney disease. Life-long medical treatment to reduce stone formation is critical in preventing chronic kidney disease and renal failure in cystinuria. In this article, we provide an overview of cystinuria with a special emphasis on medical treatment options including new agents such as alpha-lipoic acid.

**Keywords:** Nephrolithiasis, cystinuria, kidney

## INTRODUCTION

Cystinuria is a monogenic disease characterized by recurrent nephrolithiasis often starting in childhood. Cystinuria is caused by mutations in genes encoding proximal tubule dibasic amino acid transporter which facilitates reabsorption of cysteine, ornithine, lysine, and arginine from tubular fluid.<sup>1,2</sup> This reabsorption defect leads to very high urinary excretion of dibasic amino acids including cysteine. Although these amino acids generally have good solubility, cysteine can dimerize to form cystine that has poor water solubility at physiological urine pH and cause recurrent stones.<sup>3</sup> Patients with cystinuria are at increased risk for chronic kidney disease (CKD) and potentially renal failure. Thus, lifelong preventive medical treatment is often necessary in majority of the patients. This article provides an overview of cystinuria with a special focus on current medical treatment options including agents in clinical and preclinical development.

## Epidemiology

Cystinuria is the most common cause of monogenic kidney stone disease accounting for 1%–2% of adult and 6%–8% of pediatric nephrolithiasis. It affects 1 in 7000 people in the United States, though reported cystinuria prevalence highly varies in different populations (1 in 2500–100 000).<sup>4</sup> The true prevalence of cystinuria is predicted to be higher considering that some affected individuals rarely form stones and thus may not be getting the diagnostic urine studies or stone analysis.<sup>4</sup> Majority of cystinuria patients present in childhood (~75% within the first decade) with the mean age of first stone detection at 13 years. In general, there are no sex differences in age of disease onset; however, boys were reported to more frequently present with stones within the first 3 years of life.<sup>5</sup>

## Pathophysiology

The cysteine transporter is a heterodimer composed of 2 subunits. The heavy subunit rBAT is encoded by *SLC3A1*, and the light subunit b<sup>0</sup>+AT is encoded by *SLC7A9*.<sup>6</sup> The defects in this transporter cause impaired reabsorption of cysteine that results in hyperexcretion of cystine in the urine (>300 mg/day compared to <30 mg/day in healthy subjects).<sup>3</sup> In addition to the kidney tubules, the dibasic amino acid transporter is also expressed in intestinal epithelial

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cells causing impaired intestinal cysteine absorption in cystinuria patients. However, this intestinal defect does not cause any clinical manifestations since there are alternative pathways for cysteine absorption in the gut.<sup>7</sup>

Cystine has poor solubility at physiological urine pH and its solubility dramatically increases in alkaline urine. At pH 7, cystine solubility is ~250 mg/L which increases to 500 and 1000 mg/L at pH of 7.5 and 8, respectively.<sup>8</sup> Urine volume and pH are the key determinants of cystine solubility, whereas dietary protein and sodium intake are important determinants of urinary cystine excretion.<sup>9</sup> Current preventive strategies are targeting these mechanisms with the goal of increasing cystine solubility and/or decreasing urinary excretion.

### Genetics

Cystinuria typically has autosomal recessive inheritance; however, autosomal dominant inheritance with incomplete penetrance has also been reported.<sup>10</sup> As mentioned above, the dibasic amino acid transporter consists of 2 subunits: neutral and basic amino acid protein rBAT (encoded by *SLC3A1* on chromosome 2p16.3) and b<sup>0</sup>+AT amino acid transporter (encoded by *SLC7A9* on chromosome 19q13.1).<sup>11</sup> Cystinuria is classified into 3 types (A, B, and AB) based on the genetic abnormality (Table 1). Type A patients have *SLC3A1* mutations, type B patients have *SLC7A9* mutations, and type AB patients have mutations in both *SLC3A1* and *SLC7A9*.<sup>10</sup> In a large Italian cystinuria cohort, the prevalence of type A, B, and AB was 45%, 53%, and 2%, respectively.<sup>5</sup> Type A cystinuria is inherited autosomal recessively and heterozygous carriers typically have normal cystine excretion. Among *SLC3A1* mutations, p.Met467Thr is the most frequent one, accounting for ~30% of the known mutant alleles. Other common *SLC3A1* mutations include p.Thr216Met and p.Arg270X accounting for 13% and 11% of mutated alleles, respectively.<sup>12</sup> Type B cystinuria is generally inherited autosomal recessively; however, autosomal dominant inheritance with incomplete penetrance was also reported. Of note, 86% of heterozygous *SLC7A9* mutation carriers have abnormal urinary dibasic amino acid levels.<sup>13</sup> p.Gly105Arg is the most commonly detected *SLC7A9* mutation (~20%) followed by p.Arg333Trp (11.5%).<sup>12</sup> Although very rare, type AB cystinuria patients have heterozygous mutations in both *SLC3A1* and *SLC7A9*. Earlier studies generally showed no differences in disease severity between type A and B patients.<sup>5,13</sup> Interestingly, some studies reported that type AB patients generally have a mild phenotype although it may be difficult to make any conclusions since this type is very rarely seen.<sup>14</sup>

**Table 1.** Genetics of Cystinuria

Mutated gene	<i>SLC3A1</i>	<i>SLC7A9</i>	<i>SLC3A1</i> and <i>SLC7A9</i>
Affected protein	rBAT	b <sup>0</sup> +AT	rBAT and b <sup>0</sup> +AT
Genotype	A	B	AB
Inheritance	AR	AR or AD with incomplete penetrance	Mixed heterozygosity
Prevalence	45%	53%	<2%
Carrier phenotype	Normal cystine excretion, rarely kidney stones	Elevated cystine excretion, rarely kidney stones	n/a (see type A or B)

AR, autosomal recessive; AD, autosomal dominant.

In addition to *SLC3A1* and/or *SLC7A9* mutations, cystinuria can also be seen due to chromosomal deletions. Hypotonia–cystinuria syndrome is caused by homozygous deletions affecting *SLC3A1* and the neighboring gene *PREPL* (prolyl endopeptidase-like) in the short arm of the second chromosome. In addition to cystinuria, this condition is characterized by hypotonia, minor facial dysmorphism, mild to moderate intellectual disability, and growth hormone deficiency.<sup>15,16</sup> Larger deletions in the same region can cause atypical hypotonia–cystinuria syndrome that generally includes deletion of *CAMKMT* (calmodulin lysine N-methyltransferase) in addition to *PREPL* and *SLC3A1*. This condition is more severe causing mitochondrial dysfunction and intellectual disability.<sup>17</sup> The most severe form is 2p21 deletion syndrome which affects *PPM1B* (protein phosphatase, magnesium-dependent, 1b) along with other genes. This condition causes the most severe phenotype and affected patients generally die within the first few years of life.<sup>15,18</sup>

### Clinical Presentation and Diagnosis

Clinical manifestations of cystinuria are similar to any patient with obstructive urolithiasis including flank pain, loin pain, gross hematuria, vomiting, or fever. Symptoms can be more variable in children and include microscopic or gross hematuria, dysuria, recurrent abdominal pain, and recurrent urinary tract infections. In small children, symptoms can be vague or non-specific such as irritability, vomiting, and unmotivated crying.<sup>2</sup> Patients with non-obstructive stones can be asymptomatic, and in these patients, stones can be detected incidentally during imaging tests.

The first step in diagnosing cystinuria is clinical suspicion. Most cystinuria patients present in childhood with an average age of first stone detection of 13 years, and cystine stones are responsible for up to 6%–8% of all pediatric kidney stones.<sup>5</sup> Thus, cystinuria should be considered in the differential diagnosis of all pediatric stone formers.<sup>4</sup> Cystinuria can also be suspected prenatally if the hyperechoic colon is visualized during routine prenatal ultrasound. This phenomenon is thought to be caused by cystine precipitation in the colon that results from high cystine concentration in the amniotic fluid exceeding the intestinal absorption capacity.<sup>19,20</sup> In adults, cystine stones are rare (~1% of all stones) due to the higher prevalence of other types of stones that are associated with obesity and dietary factors.<sup>12</sup> Thus, certain clinical information can increase suspicion of cystinuria. One of the strongest clinical elements in cystinuria is positive family history. Screening for cystinuria should be performed in patients with a positive family history or parental consanguinity.<sup>4,12</sup> In the absence of these, cystinuria should also be suspected in patients with severe stone disease including recurrent or bilateral renal stones or patients presenting with large staghorn calculi filling the collecting system (Figure 1) and requiring surgical management.<sup>21</sup>

Cystinuria can be diagnosed by stone analysis, microscopic examination of urine, or urine cystine quantification.<sup>22</sup> Although it is not always required, genetic testing may be useful in certain situations such as atypical clinical presentation, determining the mode of inheritance, and genetic counseling. Genetic testing can also be useful in diagnosing patients with a prenatally detected hyperechoic colon since urinary cystine excretion might be difficult to interpret in the neonatal period due to tubular immaturity.<sup>23</sup>



**Figure 1.** Staghorn calculi in a pediatric cystinuria patient (image courtesy of Dr. Aaron J. Krill, Children's National Hospital, Washington, D.C. We also thank the patient and family for sharing the photo with us and permitting to use).

Stone analysis is the gold standard for determining the type of kidney stone in any patient and similarly can be diagnostic in cystinuria.<sup>2,4,12</sup> Microscopic examination of the first morning urine sample can reveal pathognomonic hexagonal crystals (Figure 2), which is highly specific for cystinuria and can be seen in up to 2/3 of untreated patients.<sup>24,25</sup> For determining cystine hyperexcretion, the sodium-nitroprusside test can be used as the initial screening test. In this qualitative colorimetric test, urine displays a purple color in the presence of high cystine concentration. Although useful as a screening test, it can yield false-positive results in homocystinuria, renal Fanconi syndrome, and patients taking ampicillin or sulfa-containing drugs.<sup>10,25</sup> Thus, positive results need confirmation by quantitative chromatographic analysis of urine for cystine excretion. Measurement of 24-hour urine cystine excretion is the gold standard test for determining cystine hyperexcretion. In healthy subjects, daily urine cystine excretion is <30 mg,



**Figure 2.** Characteristic hexagonal cystine crystals in urine microscopy (licensed from GettyImages).

whereas cystinuria patients typically have >300 mg/day of cystine excretion. Heterozygote carriers have either slightly elevated or normal cystine excretion depending on the genotype as discussed above. Although it is considered the gold standard, 24-hour urine collection can be challenging in young kids, and spot urine cystine/creatinine ratio can be used to detect cystine hyperexcretion in this population. Similar to most urine metabolic tests, the upper limit of normal cystine excretion differs in different age groups which are as follows: <80 mg/g creatinine for <1 month, <52 mg/g creatinine for 1-12 months, and <35 mg/g creatinine >1 year.<sup>26</sup>

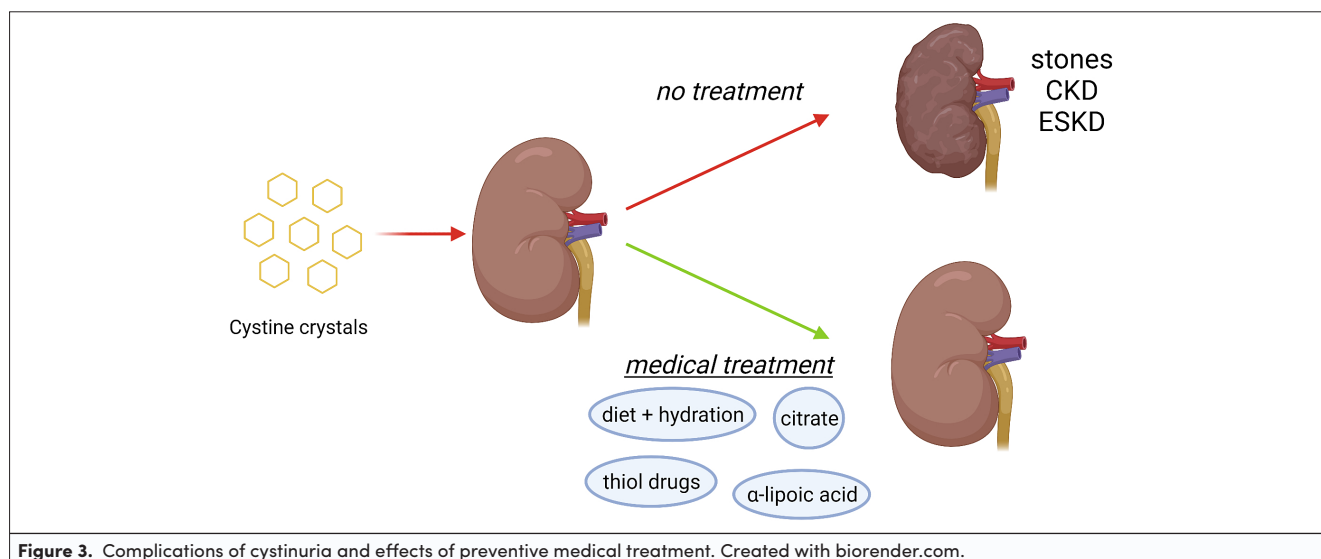
Aside from detecting kidney stones and determining the stone burden or complications (such as obstruction), imaging modalities have limited utility in diagnosing cystinuria. Cystine stones are weakly radiopaque due to their sulfur content; however, their radiopacity is less than calcium stones which makes them difficult to detect on plain x-ray.<sup>10</sup> As with other kidney stones, computed tomography (CT) scan offers the highest sensitivity and specificity; however, it is less commonly used in children due to concerns regarding radiation exposure. In children, renal ultrasound is often the first-line imaging modality, and low-dose CT can be considered in selected patients.<sup>27</sup>

### Complications and Prognosis

Nephrolithiasis is generally associated with increased risk for CKD;<sup>28</sup> however, in cystinuria patients, CKD incidence is much greater than general kidney stone population.<sup>29,30</sup> In a cohort of 314 cystinuria patients (≥16 years old), only 22.5% had normal estimated glomerular filtration rate (eGFR) (>90 mL/min/1.73 m<sup>2</sup>) and 26.7% had eGFR less than 60 mL/min/1.73 m<sup>2</sup>.<sup>29</sup> Another study in 120 cystinuria patients showed similar results where only 24.6% had normal eGFR, and 17.8% had eGFR less than 60 mL/min/1.73 m<sup>2</sup>.<sup>31</sup> In addition, end-stage kidney disease (ESKD) was reported in 5% of cystinuria patients in another study.<sup>13</sup> The key mechanism of impaired renal function in cystinuria is the insolubility of cystine in the tubular fluid and urine. At the histological level, cystine crystals can cause obstruction in the ducts of Bellini and lead to interstitial inflammation/fibrosis.<sup>22,32</sup> Over time, cycles of inflammation and fibrosis can lead to nephron dysfunction and glomerulosclerosis. In addition, recurrent surgical procedures and infections may further contribute to renal injury.<sup>32</sup> Cystinuria is also associated with a high prevalence of hypertension compared to the general nephrolithiasis population.<sup>33</sup> Earlier studies reported that 28%-50% of cystinuria patients have hypertension,<sup>30-32</sup> which is parallel to high CKD incidence. For all these reasons, frequent clinical follow-up and medical therapy to prevent cystine stone events and CKD progression are of utmost importance (Figure 3).

### MEDICAL TREATMENT OF CYSTINURIA

The overall goal of cystinuria treatment is to prevent cystine supersaturation and crystallization by promoting its solubility in the urine. Urine cystine solubility is directly related to cystine concentration and pH. Cystine concentration is determined by cystine excretion and urine volume. Dietary protein and sodium restriction primarily reduces urinary cystine excretion and high fluid intake increases urine volume. These lifestyle changes aim to keep the urinary cystine concentration below its solubility limit, whereas urinary alkalinization directly increases solubility



**Figure 3.** Complications of cystinuria and effects of preventive medical treatment. Created with biorender.com.

of cystine without affecting its excretion or concentration. A stepwise approach is used in cystinuria management.<sup>34</sup> Initial measures are increasing daily fluid intake and dietary changes (sodium  $\pm$  protein restriction). Depending on the urine pH, urinary alkalization with potassium citrate is commonly used as one of the first-line treatments. If these measures fail despite good compliance, then cystine-binding thiol drugs or newer treatments are used.

### Diet

Dietary sodium restriction can be advised for all patients since low sodium intake has been shown to reduce urinary cystine excretion in adults and kids.<sup>35</sup> In adults, recommended sodium intake is  $<2$  g/day, whereas in children  $<1$ - $1.5$  meq/kg/day is recommended.<sup>36,37</sup> Reducing dietary protein intake can also decrease cystine excretion.<sup>38</sup> In adults, recommended daily protein intake is  $<1$  g/kg (per ideal body weight).<sup>39</sup> In addition to protein restriction, reducing the cysteine precursor methionine intake has also been shown to decrease cystine excretion.<sup>34,37</sup> Animal proteins such as fish, poultry, meat, and eggs contain high amounts of methionine; thus, patients can be recommended to consume mostly non-animal proteins. Reducing animal protein intake can have additional benefits such as increasing urinary pH that enhances cystine solubility. In children, excessive protein restriction is not recommended, since it can compromise growth. However, children can avoid excessive protein intake above recommended daily allowance per age.<sup>38</sup>

### Hydration

Along with dietary changes, increasing fluid intake is generally the first step in cystinuria management. The general goal is to keep 24-hour urine cystine concentration under 250 mg/L, which is the solubility limit at physiological urinary pH of 7. Considering that most adult cystinuria patients have  $>500$ - $600$  mg/day cystine excretion, achieving urine volume of at least 2.5 L per day is recommended.<sup>34</sup> In children, fluid intake and urine output goals depend on the size of the patient. In general, 2 L/1.73 m<sup>2</sup> is the recommended minimum daily urine output goal.<sup>40</sup> One challenge of hydration treatment is ensuring patients drink water around the clock, since even

brief cystine supersaturation episodes can theoretically lead to crystallization and stone formation. For this reason, adult patients are sometimes recommended to drink fluids every 1-2 hours during the day as well as right before going to bed and at least once during the night.<sup>36</sup> However, adherence to this regimen is not always feasible and cystinuria patients report worse health-related quality of life with more frequent sleep problems and nocturia compared to other stone formers.<sup>41</sup> Effective treatments that can reduce stone recurrence with relatively lower fluid intake can have a major impact on patients' quality of life. Hydration can be monitored at home by dipstick urine specific gravity measurement with the goal of  $\leq 1.005$  in the spot morning urine.<sup>42</sup> In addition, patients can use smartphone applications to monitor water intake. In addition to water, alkaline beverages, such as mineral water that are rich in bicarbonate and low in sodium, and citrus juices can also be preferred.

### Urine Alkalinization

Urine pH is a key determinant of cystine solubility and small changes in pH can have a big impact. At urinary pH of 7, the solubility of cystine is  $\sim 250$  mg/L, which increases to 500 and 1000 mg/L at pH 7.5 and 8.0, respectively.<sup>8</sup> Urine alkalization, along with diet and fluid changes, is generally a safe and effective approach to increase cystine solubility. The treatment goal is to increase urine pH to 7.5-8.0.<sup>42</sup> Urine pH can be monitored in 24-hour collections as well as at home by urine dipsticks. In addition to preventing stone formation, alkalization can also dissolve existing cystine stones in some patients.<sup>2,36</sup> Potassium citrate or sodium bicarbonate can be used to increase urine pH. Since excess sodium intake can increase cystine excretion, potassium citrate is generally the preferred agent unless there is a contraindication, such as advanced CKD or other conditions increasing the risk for hyperkalemia.<sup>3</sup> The usual dose range for potassium citrate is 60-80 mEq/day in adults and 60-80 mEq/1.73 m<sup>2</sup> in children.<sup>39</sup> For sustained urine alkalization, it is recommended to be taken in 3-4 divided doses. The most common side effect of potassium citrate is gastrointestinal discomfort, which is generally less prominent when it is taken with a meal.<sup>10,43</sup> Compliance may be challenging in some patients due to poor taste (particularly



with liquid formulations) and frequent daily dosing. Urinary alkalinization, especially urinary pH above 7.5, is also associated with an increased theoretical risk of calcium phosphate stone formation, which requires caution.

Acetazolamide is a carbonic anhydrase inhibitor that can increase urinary bicarbonate levels and pH. However, acetazolamide can cause hypocitraturia and metabolic acidosis as side effects and generally not well tolerated. An earlier study showed that acetazolamide as an adjunct to potassium citrate was effective in increasing urinary pH.<sup>44</sup> However, extra caution must be taken as acetazolamide can facilitate calcium phosphate stone formation due to both increased urine pH and hypocitraturia.

### Cystine-Binding Thiol Drugs

Cystine-binding thiol drugs are recommended in patients who continue to have frequent stones despite conventional measures such as increased fluid intake, dietary changes, and urine alkalinization.<sup>36</sup> Most commonly used cystine-binding drugs are tiopronin and D-penicillamine, although captopril is also used in some centers. Thiol-based drugs have a sulfhydryl group that can reduce the disulfide bond between cysteine moieties and generate a complex that is more water-soluble than the cystine.<sup>3,45</sup>

### D-Penicillamine

Penicillamine is the first thiol drug used in cystinuria.<sup>45</sup> The typical recommended dose is 1-4 g/day in adults and 20-30 mg/kg/day in children (in 3-4 divided doses).<sup>39</sup> Although the US Food and Drug Administration (FDA) approved penicillamine for treatment of cystinuria, it can cause serious side effects including allergy, nausea/vomiting, lupus-like syndrome (fever, rash, arthralgias, leukopenia, and thrombocytopenia), abnormal taste, diarrhea, hepatotoxicity, proteinuria, and copper/zinc deficiency. Long-term penicillamine treatment might also lead to pyridoxine (vitamin B6) deficiency, which might require oral supplementation therapy. An earlier study showed that D-penicillamine was associated with adverse effects in 29.5% of patients which led to treatment discontinuation in 85% of these patients.<sup>29</sup> Another study that looked at adverse effects of D-penicillamine from 1970 to 2020 through the FDA Adverse Event Reporting System reported drug hypersensitivity being the most common side effect followed by dystonia, joint swelling, and pyrexia.<sup>45</sup> Another study done in Japan on 15 pediatric patients showed side effects in 85% of patients, 70% of whom ultimately discontinued penicillamine.<sup>46</sup>

### Tiopronin ( $\alpha$ -Mercaptopropionyl-Glycine)

Tiopronin is the second-generation thiol drug approved by FDA for cystinuria and the most commonly used cystine-binding agent in the United States. It is generally considered equally effective as D-penicillamine in improving cystine solubility with a slightly more favorable side effect profile. For children, the tiopronin dose is 15-40 mg/kg/day in 3 divided doses with a higher dose given at bedtime. The adult dose is 800-1500 mg/day in 3 divided doses.<sup>24,39</sup> Tiopronin needs to be taken 1 hour before or 2 hours after the meal. An enteric-coated formulation of tiopronin was released in 2019, which can be taken irrespective of food intake and requires less number of pills to be taken by patients.<sup>43</sup> Similar to penicillamine, tiopronin can cause

serious side effects including rash, arthralgia, exanthema, pemphigus, thrombocytopenia, polymyositis, proteinuria, and nephrotic syndrome. A study done in France showed that 24.6% of patients reported some sort of side effects which led to 68% of patients' treatment discontinuation, which was slightly lower than the discontinuation rate of penicillamine (84.6%).<sup>42</sup>

### Captopril

Captopril is the first FDA-approved angiotensin-converting enzyme inhibitor.<sup>47</sup> It has a sulfhydryl group that can form a bond with cysteine, and it has been used off-label in cystinuria.<sup>48-50</sup> The recommended dose in adults is 150 mg/day and in children 1.5-6 mg/kg/day in 3 divided doses.<sup>10,47</sup> Since captopril has blood pressure-lowering and antiproteinuric effects, it can be the treatment of choice for patients with cystinuria and hypertension  $\pm$  proteinuria). Adverse effects include hyperkalemia, acute kidney injury, cough, and hypotension.

## NEW TREATMENTS

### Crystal Growth Inhibitors

These compounds were identified after the determination of the cystine crystal growth process by real-time in situ atomic force microscopy. Cystine mimicking diamides, such as cystine dimethyl ester, were shown to inhibit cystine stones growth in vitro and in a mouse model of cystinuria.<sup>51</sup> Follow-on studies identified novel cystine diamides including cystine bis(*N*-methylpiperazine) with improved stability and bioavailability.<sup>52</sup> Currently, these compounds are in preclinical development.<sup>3</sup>

### Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a nutritional supplement commonly used for diabetic neuropathy as an antioxidant.<sup>53</sup> It was recently shown to increase cystine solubility and prevent stone formation in a mouse model of cystinuria.<sup>54</sup> Although its mechanism of action is not clear, ALA is thought to increase cystine solubility via unidentified metabolites excreted in the urine. In our center, we used ALA successfully in 2 pediatric cystinuria patients (6 and 15 years old).<sup>55</sup> These patients were started on ALA in addition to conventional measures (diet, fluid, and potassium citrate) which resulted in rapid improvements in markers of urine cystine solubility (cystine supersaturation and capacity). In one patient, urine cystine capacity improved from -222 to +26, and cystine supersaturation improved from 1.7 to 0.88, in the absence of any major changes in urine volume, pH, or cystine excretion (Table 2). In the other patient, existing cystine stones disappeared after ALA initiation, which suggests that ALA can potentially help dissolving existing stones. The ALA dose used in our center is 30 mg/kg/day in 2 divided doses (maximum daily dose 1200 mg). At this dose, our patients have not reported any side effects, and their complete blood count and chemistry panels were normal during the 3-year monitoring period. The safety of ALA has been extensively documented in clinical trials for diabetic neuropathy. The most frequent adverse effect is dose-dependent nausea. The less frequent side effects include vomiting and vertigo which affect >5% of patients at doses up to 1200 mg/day.<sup>56</sup> Currently, a phase 2 randomized placebo-controlled clinical trial is investigating the efficacy of ALA in stone recurrence in adult cystinuria patients (clinicaltrials.gov ID: NCT02910531). Table 3 summarizes current treatment options for cystinuria.

**Table 2.** Twenty-Four-Hour Urine Test Results of a Pediatric Patient Before and After Alpha-Lipoic Acid Therapy<sup>55</sup>

Treatment	Volume (L)	pH	Cystine (mg)	Cystine Supersaturation	Cystine Capacity (mg/L)	Creatinine (mg/kg)
Baseline	0.75	7.44	408	1.7	-223	21.6
Baseline	1.28	7.20	632	1.63	-226	23.1
Citrate	1.08	7.39	630	1.7	-222	21.8
Citrate+ALA (low dose)	1.42	7.53	464	1.09	-62	18.9
Citrate+ALA (high dose)	2.13	7.31	587	0.88	-1	19.2
Citrate+ALA (high dose)	1.73	7.31	489	1.01	26	18.6

ALA, alpha-lipoic acid.

### Vasopressin Antagonists

Tolvaptan is a vasopressin type 2 receptor antagonist approved by the FDA for the treatment of rapidly progressive ADPKD (autosomal dominant polycystic kidney disease) and hyponatremia associated with the syndrome of inappropriate antidiuretic hormone secretion. It primarily works by blocking the antidiuretic hormone effect in the kidney and commonly causes polyuria, which can theoretically reduce cystine concentration in the urine. An earlier pilot study with 2 cystinuria subjects showed that 4-day tolvaptan treatment can reduce urine cystine concentration below the solubility limit.<sup>57</sup> A recent pilot study in 4 cystinuria subjects showed that a short course of tolvaptan for 8 days can increase urine volume which leads to reduced cystine concentration and thus improved cystine solubility markers.<sup>58</sup> However, the patients reported extreme thirst with tolvaptan treatment, which suggests that long-term

treatment compliance might be problematic. In addition, tolvaptan is associated with hepatotoxicity that requires frequent monitoring.<sup>59</sup> Due to these concerns, it is unclear whether it will be a feasible treatment option for cystinuria. In addition, long-term clinical studies to show sustained efficacy and tolerability of tolvaptan in cystinuria patients are required.

### MONITORING FOR TREATMENT ADEQUACY

The effectiveness of medical treatment is recommended to be monitored by 24-hour urine tests.<sup>55</sup> The key disease markers to follow are urine volume, cystine excretion, and pH. In addition, cystine supersaturation and cystine capacity are markers of cystine solubility; however, these tests are currently available in the United States only. Cystine excretion and urine volume provide information about average cystine concentration

**Table 3.** Medications and Supplements Used in Cystinuria

	Mechanism	Dose	Side Effects
<b>Potassium citrate</b>	Urine alkalinization	<i>Children:</i> 60-80 mEq/1.73 m <sup>2</sup> /day <i>Adults:</i> 60-80 mEq/day Frequency: 3-4 times per day	Gastrointestinal side effects. Hyperkalemia can be dose-limiting in patients with advanced CKD (consider sodium bicarbonate).
<b>Penicillamine</b>	Thiol drug, increases cystine solubility	<i>Children:</i> 20-30 mg/kg/day max dose 4000 mg/day <i>Adults:</i> 1-4 g/day Frequency: 3-4 times per day	Fever, rash, loss of taste, arthritis, leukopenia, aplastic anemia, gastrointestinal disturbance, membranous nephropathy with proteinuria, copper/zinc and pyridoxine deficiency
<b>Tiopronin</b>	Thiol drug, increases cystine solubility	<i>Children:</i> 15-40 mg/kg/day max dose 1500 mg/day <i>Adults:</i> 800-1500 mg/kg/day Frequency: 3 times per day	Similar side effects as D-penicillamine with slightly less prevalence.
<b>Captopril</b>	Thiol drug, increases cystine solubility	<i>Children:</i> 1.5-6 mg/kg/day max dose 150 mg/day <i>Adults:</i> 75-150 mg/day Frequency: 3 times per day	Acute kidney injury, hyperkalemia, hypotension, cough
<b>Alpha-lipoic acid</b>	Increases cystine solubility	<i>Children:</i> 30 mg/kg/day max dose 1200 mg/day <i>Adults:</i> 1200 mg/day Frequency: 2 times per day	Nausea, vomiting, vertigo

CKD, chronic kidney disease.

in the urine, which is recommended to be kept under solubility limit (250 mg/L) at physiological urine pH. Urine pH is recommended to be kept around 7.5 to increase cystine solubility; however, clinicians should be aware of increased calcium phosphate stone formation risk at high pH. Cystine supersaturation is a crystallization marker with values under 1.0 suggesting that urine is undersaturated for cystine.<sup>60</sup> In patients using cystine-binding drugs, cystine concentration and supersaturation become unreliable due to the chemical interactions between these drugs and cystine. Cystine capacity is another marker of cystine solubility which is not affected by cysteine-binding drugs, and positive capacity values suggest that urine is undersaturated.<sup>61</sup> However, the therapeutic goals for cystine supersaturation and capacity that correlate with reduced stone recurrence are subject to debate.<sup>62</sup>

## CONCLUSION

Cystinuria is a severe, hereditary form of kidney stone disease. Lifelong preventive treatment is often indicated in majority of patients to prevent complications such as CKD and ESKD. There are several treatment options available; however, some are with serious side effects. There is an unmet medical need for newer treatment agents with good efficacy and minimal adverse effects for long-term use.

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