

MINI-REVIEW

Cystinuria: Review of a Life-long and Frustrating Disease

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Cystinuria, accounting for about 1-2% of kidney stones in adults, carries significant morbidity beginning at a young age [1]. Cystine stone formers have more stone events compared to other stone formers, as well as more surgical interventions, potentially contributing to faster progression to chronic kidney disease (CKD), and end-stage kidney disease (ESKD) [2]. Successful medical therapy for cystine stone formers may be limited by adherence to the extensive lifestyle changes and the adverse side effect profiles of some interventions, leading to decreased quality of life for these patients relative to other stone formers.

Cystinuria is a rare genetic disorder characterized by high urine cystine excretion and kidney stone formation and is a life-long disease.

PATHOPHYSIOLOGY

Cystine is a homo-dimer of the amino acid cysteine. Cystine transport occurs within the proximal tubule of the nephron and its transepithelial transporter is also responsible for the transport of the dibasic amino acids ornithine, lysine, and arginine (COLA). This transporter is also found within the gastrointestinal (GI) tract, though this aspect has no known significance with regard to pathology of the disease [3]. The transporter consists of two subunits linked by a disulfide bond, rBAT and b0,+AT1 and functions by binding to the dibasic molecule cystine within the lumen of the proximal tubule where it is then

reduced to individual cysteine molecules before returning to the bloodstream. Normal excretion of cystine is <30mg/day, while those with the defective transporter excrete at least 400mg/day and even as much as 3600mg/day [4].

Cystinuria is caused by a genetic defect within this transporter. Two known mutations involve SLC3A1 and SLC7A9, though up to 5% of patients do not have an identified mutation [5]. A novel transporter, AGT1, in a distal segment of the proximal tubule, has been recently found in mice to be involved in the transport of cystine, which could explain unidentified mutations in humans causing cystinuria [6]. SLC3A1 encodes for rBAT. Patients with this mutation are classified as type A cystinuria. While the most common mutation involves a substitution mutation resulting in defective transport of the transporter to the membrane, there are more than 575 other identified mu-

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Abbreviations: CKD, Chronic kidney disease; ESKD, end-stage kidney disease; COLA, cystine-ornithine-lysine-arginine; GI, gastrointestinal; ICC, International Cystinuria Consortium; CT, computerized tomography; ESWL, extracorporeal shockwave lithotripsy; CBC, complete blood counts; LFT, liver function tests; eGFR, estimated glomerular filtration rate; ALA, α -lipoic acid.

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tations [7]. SLC7A9 is responsible for encoding the other subunit, b0,+AT1. Patients with this mutation are classified as having type B cystinuria. Patients may also be classified as having type AAB or ABB cystinuria, where an individual would carry a defect in both of these genes. The International Cystinuria Consortium (ICC) estimates that 38% of their subjects are type A, 47% type B, and 14% type AAB or ABB [3]. Although holding promise to possible individualized medicine in the future, this classification scheme currently holds little phenotypic or clinical significance.

The pattern of inheritance for these mutations is recessive. However, studies in SLC3A1 knockout mice demonstrated that approximately 82% at age 1 month, and 2% at 1 year had no cystine stones, suggesting a possibility that there are environmental and epigenetic effects causing incomplete penetrance in humans [5].

EPIDEMIOLOGY

World-wide prevalence of the disease is about 1:7,000, but significant ethnic variations exist. Libyan Jewish people in particular have higher occurrences of the disease, whereas the rates in the Swedish population are 1:100,000 [8]. Cystine stones account for about 1-2% of adult stones and 6-8% of pediatric stones [9].

Average age of clinical presentation is around 12 years, with boys typically presenting earlier than girls. It is possible for cystinuria to present during later decades in life, especially in heterozygotes who might only present during moments of dehydration when cystine crystallization is possible. Men are also more likely to have more severe presentations of the disease with twice as many stone events per year compared to women [10]. As such, men tend to have more interventions and episodes of acute kidney injury, potentially leading to more rapid CKD progression.

CLINICAL PRESENTATION AND DIAGNOSIS

As with other stones, cystine stones can present with flank pain radiating to the groin, hematuria, dysuria, as well as systemic symptoms such as nausea and vomiting.

Diagnosis of the acute event is typically with imaging by ultrasound or computerized tomography (CT) and is not specific to cystinuria. Though plain radiographs may miss cystine stones as they are radiolucent (unless co-precipitating with calcium), they are easily visualized on CT scans. Large staghorn calculi, bilateral stone disease, and presentation in childhood should raise suspicion for a genetic etiology of stone disease.

The diagnosis of underlying cystinuria can be made with urinalysis and microscopic evaluation, which may



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Figure 1. Classic Hexagonal Appearance of Cystine Crystals on Urine Microscopy

reveal hexagonal crystals (Figure 1). Though highly specific if present, the absence of crystals does not exclude disease given sensitivity rates as low as 25% in pediatric patients [11]. If evaluation for crystals is not performed on presentation or crystals are not visualized, a qualitative cyanide-nitroprusside screen can be done. Addition of the solution to urine produces a purple color, revealing the presence of >75mg/L of cystine excretion (normal is <30mg/L). Sensitivity for this test is around 75% and involves toxic reagents, making this screening modality less favored among some clinicians [12]. A total cystine measurement on a 24-hour urine collection, although more challenging to perform for pediatric patients, is the most widely used form of testing. It can be used to quantify cystine excretion and extrapolate this to future fluid intake goals, as well as determine if more aggressive medical intervention is warranted. Stone analysis by infrared spectroscopy and X-ray diffraction is considered the gold standard for diagnosis by most societies [13].

Genetic testing is currently not widely recommended, although some societies including the Metabolic Nephropathy Joint Working Group of the European Reference Network for Rare Kidney Diseases have released recommendations including genetic testing as part of genetic counseling for families [13].

TREATMENT

In the acute setting, treatment of cystine stones is very similar to treatment of other stones, with hydration and analgesia being the usual treatment. Based on the size

Table 1. Pharmacologic and Lifestyle Interventions in the Treatment of Cystinuria

	Class of Intervention	Example of Intervention	Mechanism of Action	Side Effects
Recommended for all patients with symptomatic cystinuria	Lifestyle changes	Increased fluid intake Decreased protein intake Decreased salt intake	Decrease the concentration of cystine below the solubility	Significant reduction in protein intake not recommended in pediatric patients.
	Alkalinizing agents	Potassium citrate Sodium bicarbonate	Alkalinization of urine to increase cystine solubility	Abdominal pain, nausea, vomiting. Sodium bicarbonate is preferred in patients with renal insufficiency.
Recommended for patients with persistent nephrolithiasis despite above measures or high levels of cystine excretion	Cystine-binding thiol drugs	D-penicillamine Tiopronin	Reduction of cysteine and binding to free cystine	Nausea, diarrhea, rash, oral ulcers, abnormal taste, arthritis, cytopenias, nephrotic syndrome, copper and zinc deficiency, and liver toxicity. Vitamin B6 deficiency with use of D-penicillamine.

Acetazolamide and captopril are **no longer recommended** due to lack of efficacy as well as side effect profile.

of the stone and its location, conservative management or surgical intervention may be warranted. Stones with signs of infection or severe obstruction should undergo decompression with stent or nephrostomy placement with subsequent targeted management of the stone. In terms of definitive interventions, retrograde ureteroscopic stone retrieval is preferred, followed by percutaneous nephrolithotomy for larger stones, with exceedingly rare need for open surgery or nephrectomy for very large stones [14]. Extracorporeal shockwave lithotripsy (ESWL) is not recommended given lack of efficacy for cystine stones [15].

The ultimate goal for treatment of patients with symptomatic cystinuria is to reduce the urine cystine concentration below the solubility limit for cystine through higher urine volumes and higher urine pH, as cystine solubility increases at alkaline urine pH (Table 1). Generally, patients are instructed to maintain urine output of at least 3L/day, thus necessitating fluid intake at least 3.5-4L/day. Individualized recommendations are based on total daily cystine excretions which are used to calculate volumes necessary to reduce cystine concentrations to below 250mg/L at a pH of 7 [16]. It is important to emphasize that a large fluid bolus should be taken before sleep due to the diurnal variation of cystine excretion. Prot-Bertoy et al. demonstrated in a group of 89 patients, presence of cystine crystalluria was found in <20% of patients with a goal specific gravity of <1.005, regardless of urine pH [17]. This makes specific gravity a good marker of urine output goal, particularly in highly motivated patients.

Alkalinization of urine is predominately done with potassium citrate (60-80mEq, divided into 3 or 4 dosages per day) [18]. Sodium bicarbonate is an alternative alkalinizing agent when patients are not able to tolerate

potassium citrate or in cases of severe renal insufficiency. However, it is not the preferred agent given the sodium load that is ideally avoided. Patients are educated on using pH test strips at home to titrate their alkalinizing therapy to a pH goal of 7.5-8. Unfortunately, at higher urine pH comes the risk of calcium phosphate stones, thus careful titration for optimal therapeutic benefit is key.

Additional recommended lifestyle changes to minimize the number of stone events include a low sodium and low protein diet. Although the cystine transporter is largely sodium-independent, it is thought that high sodium diets increase cystine excretion. Furthermore, higher urinary sodium is associated with hypercalciuria, so limiting dietary sodium is advisable to prevent formation of calcium phosphate stones, which can also be seen in patients with cystinuria, particularly with treatment. A diet of 1-1.5mEq sodium/kg/day is recommended in children, while adults are counselled to limit intake to <80-100mEq per day [13]. Patients are also recommended to limit daily protein intake to less than 1g/kg as the breakdown of methionine leads to an increased production of cystine, as well as lowering the pH of urine by increasing acid production. However, this recommendation is not realistic in pediatric patients so as to not restrict growth [19].

When these conservative measures are not sufficient to reduce or prevent stone events, or when 24-hour urine collection reveals extremely high levels of cystine excretion, thiol-based interventions should be considered. Two medications within this class of drugs include tiopronin and D-penicillamine. They function by splitting the disulfide bond between cysteine molecules, making it more soluble in urine. As discussed further below, there are several potential side effects from this class of drugs

including nausea, diarrhea, rash, oral ulcers, abnormal taste, arthritis, cytopenias, nephrotic syndrome, copper and zinc deficiency, and liver toxicity. Though previously advising laboratory monitoring for cytopenias and hepatotoxicity, the FDA now recommends only monitoring for signs of proteinuria [20]. D-penicillamine can also cause a vitamin B6 deficiency, thus supplementation with pyridoxine is recommended with therapy [21].

Captopril, an angiotensin receptor inhibitor, had previously been seen in *in vitro* studies to have increased cystine solubility through thiol-like properties. However, human studies did not demonstrate efficacy, and it is no longer recommended as an alternative agent [22]. Acetazolamide was another potential therapeutic option for urinary alkalinization. However, due to its adverse side effect profile and concern for potentiating risk of calcium phosphate stones, it too is not recommended for therapy [23].

Renal transplantation is curative as it replaces the defective transporters but is only employed in the setting of end-stage kidney failure.

CHALLENGES AND PROGNOSIS

Diagnostics

A quantitative measure of treatment efficacy had been elusive for some time as measurement of cystine solubility varies widely between individuals and urine pH [24]. In addition, thiol-based drugs can be deceptive in measuring cystine solubility as it is difficult to distinguish cystine bound to the drug from free cysteine. However, measurement of cystine supersaturation through the use of solid-phase assays has proven to be a reliable indicator, including in the presence of pharmacologic interventions, in order to titrate treatments to minimize stone events as well as unwanted drug side effects [25]. This assay is done by adding and incubating cystine crystals with sample urine to allow an equilibrium between solid and liquid phases of cystine to be reached. This is followed by measurement of the amount of precipitate formed. Formation of more precipitate than the added cystine is indicative of supersaturated urine, meaning more prone to formation of stones, while solid cystine dissolving in the urine represents undersaturated urine, which is the goal of treatment. Unfortunately, few centers in the United States are able to perform such assays, making these techniques difficult to utilize in some clinical settings.

Treatment

Predictably, patient compliance with the aforementioned treatment methods is a major obstacle. Patients are advised to make significant lifestyle changes including large amounts of volume intake, dietary restrictions, as

well as continuous monitoring of urine goals and parameters. This is particularly a challenge in pediatric patients, who make up a large proportion of this patient population. In very young children, fluid goals at times can only be met once alternative enteral feeding methods such as nasogastric tubes or gastrostomy tubes are placed. Per Pietrow et al., only 15% of patients were able to meet cystine concentration goals of <300mg/L, while a majority were only transiently successful [26].

In terms of medical intervention, the side effect profile of some drugs as well as their dosing requirements are a hindrance to compliance. For example, limiting factors in potassium citrate tolerability are gastrointestinal side effects, plus most patients require three-to-four times a day dosing for proper alkalinization. As discussed above, thiol-containing medications such as tiopronin and D-penicillamine contain several potential side effects. Prot-Bertoye et al. in a study of French patients found reports of adverse reactions to be 81.2% and 78.1% in patients treated with tiopronin and D-penicillamine, respectively, however, adverse events from tiopronin resulted in less discontinuation of therapy, meaning it was likely more tolerated than D-penicillamine. During this study, gastrointestinal, nephrotic, and mucocutaneous lesions were the most common adverse reactions [17]. If tolerated, however, these medications have been shown to be effective in preventing stone formation in 70% of patients [27].

Even with patient compliance and optimal management, stone events may still occur resulting in lower quality of life compared even to other stone-forming groups. Patients with cystine stones tend to need a longer time to recover, require more surgical interventions, and have more stone events per year. Within cystine stone formers, though, per Modersitzki et al., patients treated with tiopronin tended to have better quality of life measures than non-treated patients, demonstrating that if they can tolerate the side effects, patients tend to do better taking thiol-containing drugs [28].

Complications

Hypertension is a very common complication of cystinuria, seen in up to half of patients [29]. When treated, this further adds to the pill burden of these patients. Deterioration in kidney function is another concerning complication, with as many as 26.8% developing stage 3 CKD with an estimated glomerular filtration rate (eGFR) of <60mL/min/1.73m², and a small proportion progressing to end-stage kidney disease (ESKD) [30]. This further complicates treatment as thiol agents should be discontinued once the eGFR <60mL/min/1.73m², thus limiting use of therapeutics associated with improved quality of life.

FUTURE DIRECTIONS

Although treatment for this disease is currently a challenge for both the physician and the patient, there are promising new therapies that demonstrate the potential to reduce stone events and improve quality of life for patients without the side effects of current therapies. For example, L-cystine and α -lipoic acid (ALA) were both promising in mice studies to make cystine more soluble in urine [21,31]. ALA is currently undergoing Phase 2 trials in humans [32]. Selenium, another over-the-counter agent, demonstrated some benefit in a small study in the Middle East [33]. Bucillamine, a medication used for rheumatoid arthritis in Japan, demonstrated promise and is potentially more effective in reducing stones than tiopronin and is currently in Phase 2 trials as well [34]. Recombinant human enzymes and cystine growth inhibitors are also undergoing exploration in early trials as potential treatments. Chaperone therapies, aimed at preventing proteins from misfolding, are a potential unexplored therapy that holds promise as several mutations in cystinuria are linked with misfolding events [7].

SUMMARY

Cystinuria is a predominantly autosomal recessive disease of COLA transport in both the GI tract and the proximal tubule, resulting in formation of debilitating cystine stones that bring about significant complications including hypertension and CKD, as well as reduced quality of life for those affected. Treatment for this disease at this time include behavioral modifications, urinary alkalinization, as well as thiol-containing drugs, the latter limited by a significant side effect profile. However, patients who can tolerate these medications and remain compliant tend have fewer stone events, and thus, better quality of life measures. Although therapies are currently limited, new research developments, including molecular treatments, are on the horizon and may alter the treatment paradigm.

REFERENCES

- Leusmann DB, Blaschke R, Schmandt W. Results of 5,035 stone analyses: a contribution to epidemiology of urinary stone disease. *Scand J Urol Nephrol*. 1990;24(3):205–10.
- Worcester EM, Coe FL, Evan AP, Parks JH. Reduced renal function and benefits of treatment in cystinuria vs other forms of nephrolithiasis. *BJU Int*. 2006 Jun;97(6):1285–90.
- Rogers A, Kalakish S, Desai RA, Assimos DG. Management of cystinuria. *Urol Clin North Am*. 2007 Aug;34(3):347–62.
- Palacin M, Goodyer P, et al. Cystinuria. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The Metabolic and Molecular Basis of Inherited Disease*. 8th ed. New York: McGraw-Hill; 2001. p. 4909.
- Sahota A, Tischfield JA, Goldfarb DS, Ward MD, Hu L. Cystinuria: genetic aspects, mouse models, and a new approach to therapy. *Urolithiasis*. 2019 Feb;47(1):57–66.
- Nagamori S, Wiriyaerkmul P, Guarch ME, Okuyama H, Nakagomi S, Tadagaki K, et al. Novel cystine transporter in renal proximal tubule identified as a missing partner of cystinuria-related plasma membrane protein rBAT/SLC3A1. *Proc Natl Acad Sci USA*. 2016 Jan;113(3):775–80.
- Chillarón J, Font-Llitjós M, Fort J, Zorzano A, Goldfarb DS, Nunes V, et al. Pathophysiology and treatment of cystinuria. *Nat Rev Nephrol*. 2010 Jul;6(7):424–34.
- Claes DJ, Jackson E. Cystinuria: mechanisms and management. *Pediatr Nephrol*. 2012 Nov;27(11):2031–8.
- Eisner BH, Goldfarb DS, Baum MA, Langman CB, Curhan GC, Preminger GM, et al. Evaluation and medical management of patients with cystine nephrolithiasis: a consensus statement. *J Endourol*. 2020 Nov;34(11):1103–10.
- Dello Strologo L, Pras E, Pontesilli C, Beccia E, Ricci-Barbini V, de Sanctis L, et al. Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. *J Am Soc Nephrol*. 2002 Oct;13(10):2547–53.
- Thomas JC, DeMarco RT, Donohoe JM, Adams MC, Brock JW 3rd, Pope JC 4th. Pediatric ureteroscopic stone management. *J Urol*. 2005 Sep;174(3):1072–4.
- Daga S, Palit V, Forster JA, Biyani CS, Joyce AD, Dimitrova AB. An Update on Evaluation and Management in Cystinuria. *Urology*. 2021 Mar;149:70–5.
- Servais A, Thomas K, Dello Strologo L, Sayer JA, Bekri S, Bertholet-Thomas A, et al.; Metabolic Nephropathy Workgroup of the European Reference Network for Rare Kidney Diseases (ERKNet) and eUROGEN. Cystinuria: clinical practice recommendation. *Kidney Int*. 2021 Jan;99(1):48–58.
- Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: current concepts and future directions. *Clin Nephrol*. 2015 Mar;83(3):138–46.
- Landau EH, Shenfeld OZ, Pode D, Shapiro A, Meretyk S, Katz G, et al. Extracorporeal shock wave lithotripsy in prepubertal children: 22-year experience at a single institution with a single lithotripter. *J Urol*. 2009 Oct;182(4 Suppl):1835–9.
- van Hoeve K, Vermeersch P, Regal L, Levtchenko E. Necessity of fractionated urine collection for monitoring patients with cystinuria. *Clin Chem*. 2011 May;57(5):780–1.
- Prot-Bertoye C, Lebbah S, Daudon M, Tostivint I, Jais JP, Lillo-Le Louët A, et al.; French Cystinuria Group. Adverse events associated with currently used medical treatments for cystinuria and treatment goals: results from a series of 442 patients in France. *BJU Int*. 2019 Nov;124(5):849–61.
- Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalization of urine in homozygous cystinuria. *Urol Res*. 2001 Oct;29(5):295–302.
- Rodman JS, Blackburn P, Williams JJ, Brown A, Pospischil MA, Peterson CM. The effect of dietary protein on cystine excretion in patients with cystinuria. *Clin Nephrol*. 1984 Dec;22(6):273–8.
- Thiola EC. [package insert]. San Antonio, TX: Mission

- Pharmcal Company; 2019.
21. Rezaee ME, Rule AD, Pais VM Jr. What are the main challenges to the pharmacological management of cystinuria? *Expert Opin Pharmacother*. 2020 Feb;21(2):131–3.
 22. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, De-nu-Ciocca CJ, Matlaga BR, et al.; American Urological Association. Medical management of kidney stones: AUA guideline. *J Urol*. 2014 Aug;192(2):316–24.
 23. Sterrett SP, Penniston KL, Wolf JS Jr, Nakada SY. Acetazolamide is an effective adjunct for urinary alkalization in patients with uric acid and cystine stone formation recalcitrant to potassium citrate. *Urology*. 2008 Aug;72(2):278–81.
 24. Nakagawa Y, Asplin JR, Goldfarb DS, Parks JH, Coe FL. Clinical use of cystine supersaturation measurements. *J Urol*. 2000 Nov;164(5):1481–5.
 25. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. *Kidney Int*. 2006 Mar;69(6):1041–7.
 26. Pietrow P, Auge BK, Weizer AZ, Delvecchio FC, Silverstein AD, Mathias B, et al. Durability of the medical management of cystinuria. *J Urol*. 2003 Jan;169(1):68–70.
 27. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercapto-propionylglycine. *J Urol*. 1986 Nov;136(5):1003–8.
 28. Modersitzki F, Goldfarb DS, Goldstein RL, Sur RL, Penniston KL. Assessment of health-related quality of life in patients with cystinuria on tiopronin therapy. *Urolithiasis*. 2020 Aug;48(4):313–20.
 29. Kum F, Wong K, Game D, Bultitude M, Thomas K. Hypertension and renal impairment in patients with cystinuria: findings from a specialist cystinuria centre. *Urolithiasis*. 2019 Aug;47(4):357–63.
 30. Prot-Bertoye C, Lebbah S, Daudon M, Tostivint I, Bataille P, Bridoux F, et al.; French Cystinuria Group. CKD and its risk factors among patients with cystinuria. *Clin J Am Soc Nephrol*. 2015 May;10(5):842–51.
 31. Wiener SV, Chi T, Stoller ML. Alpha lipoic acid as a novel therapeutic approach to cystinuria. *Expert Opin Orphan Drugs*. 2018;6(4):295–300.
 32. US National Library of Medicine. Lipoic acid supplement for cystine stone (ALA). NCT02910531. [cited 2021 May 17]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02910531>. Published 2016.
 33. Mohammadi M, Shohani A, Khorami H, Nouri Mahdavi K, IzadPanahi MH, Alizadeh F, et al. The effect of selenium supplementation on cystine crystal volume in patients with cystinuria. *Biomedicine (Taipei)*. 2018 Dec;8(4):26.
 34. US National Library of Medicine. Phase 2 Multi-Center, Dose Escalation Trial To Assess The Safety And Effectiveness Of Bucillamine On Urinary Cystine Excretion And Cystine Capacity In Patients With Cystinuria. NCT02942420. [cited 2021 May 17]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02942420>. Published 2016.