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Cystinuria—Diagnosis and Management

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Abstract

Cystinuria is an autosomal recessive disorder of cystine and dibasic amino acid transport across the luminal membrane of proximal tubule and small intestine. Two responsible genes have been identified: mutations in the *SLC3A1* gene, located on the chromosome 2p, cause cystinuria type I, while variants in *SLC7A9* have been demonstrated in non-type I cystinuria. The poor urinary solubility of cystine can lead to stone formation in affected individuals which typically manifests in the second and third decades of life. Typical management involves copious oral fluid intake, urinary alkalisation and thiol medications to decrease the urinary cystine concentration below 300 mg/l. Recurrent stone formation necessitates repeated urological interventions. Fortunately, contemporary minimally invasive approaches to stone treatment are applicable in the treatment of cystine stones. The management of cystinuria is often challenging and requires a close co-operation between radiologist, nephrologist and urologist.

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1. Introduction

Cystinuria is a rare but important cause of urinary stone disease. It is an autosomal recessive defect in amino acid transport manifest in the formation of cystine urinary calculi [1]. Amino acids are freely filtered by the glomerulus and are almost completely re-absorbed by proximal tubular cells. In normal individuals 0.4% of filtered cystine is lost in the urine [2]. Two transport mechanisms, a high and a low-affinity system, are responsible for cystine re-absorption in the proximal tubular cells. In cystinuria the absorption of cystine, along with the three other dibasic amino acids, ornithine, arginine & lysine, via the high affinity process is reduced [3,4]. It is the insolubility of cystine that leads to the pathological process of calculus formation.

This article will review the current knowledge of the genetic basis of cystinuria, outline the pathophysiology of the disease and highlight treatment strategies.

2. Incidence

Approximately 1% of adult and 6% of paediatric stones are cystine [5]. The prevalence of cystinuria globally is 1 per 7000 with widespread variation: UK

1:2000; Australia 1:4000; Japan 1:18 000; Sweden 1:100 000; Libyan Jews 1:2500. Incidence is equal between the sexes but men may be more severely affected [6,7]. Although the peak incidence of first cystine calculus is 22 years of age, almost 1/4 of cytinurics will develop stones in the first decade of life with 30–40% of patients having their first stone in the teenage years [8].

3. Pathophysiology

In addition to the renal tubular malfunction of cystinuria cystine absorption from the intestine is impaired [9]. Cystine deficiency is not clinically significant since the absorption of cystine is unaffected. The clinical picture of cystinuria therefore remains a problem of stone disease.

The presence of elevated levels of urinary cystine is important due to the insolubility of cystine in urine at physiological pH. Up to pH 7 cystine solubility is approximately 250 mg/L urine whilst above pH 7.5 this will double to 500 mg/L and triple at pH 8 or greater [10]. The ionic component of urine will impact upon cystine solubility. Increasing the ionic strength of a solution from 0.005 to 0.3 will permit an additional 70 mg of additional cystine to be absorbed per litre of solution [11]. The nature of the electrolyte component of this ionic solution is also important, calcium chloride increasing solubility to a greater extent than magnesium chloride and sodium chloride respectively [11].

4. Genetics

Cystinuria is an autosomal recessive disease formally classified into 3 subtypes summarised in Table 1 [12,13]. Clinical classification of cystinuria requires the measurement of urinary cystine levels in patients (Table 2).

The first cystinuria gene SLC3A1 encodes the glycoprotein rBAT subunit of the heterodimer transporter in intestinal and renal epithelial cells, located on chromosome 2 (2p21) [14]. SLC3A1 is expressed in cells of the proximal tubules (segment$_1$ to segment$_3$). Up to 80 mutations of SLC3A1 are described in cystinuria [13,15]. Most mutations of this gene tend to be population-specific. The M467T mutation for example accounted for 40% of mutations in a cohort of Spanish families but was rare in patients studied in Quebec, Canada [15,16].

A second cystinuria gene SLC7A9 on chromosome 19 (19q13) encodes the light chain b$^{0,+}$ AT. Mutations of this gene probably cause non-type I cystinuria [17]. Multiple mutations of this gene are reported, G105R is the most common mutation [15]. The most common described in a group of Libyan Jews resulted in methionine replacing the valine amino acid residue (V170M) in the transcribed protein. In heterozygotes with the V170M mutation, urinary cystine concentrations range from 86 to 1238 micromol/g of creatinine. Some V170M heterozygotes excrete cystine in the range consistent type III disease and others with type II disease [17,18]. Recently, Dello Strologo et al. [19] have proposed a new genetic classification, as follows:

Table 2 – Urinary cystine concentration

Normal	<30 mg/day (0.13 mmol/day)
Homozygote Cystinuria Majority form stones	>400 mg/day (1.7 mmol/day)
Heterozygote Type I Do not form stones	<200 mg/day (0.8 mmol/day)
Heterozygote Type II & III May form stones	200–400 mg/day (0.8–1.7 mmol/day)

Table 1 – Sub-classification of cystinuria by genetic characteristics

Rosenberg et al. [12]		Type I	Type II	Type III
Molecular		Type I	Non–Type I	
Urinary cystine, lysine, arginine & ornithine in heterozygotes Active intestinal transport in homozygotes		Normal	Elevated	Elevated
Cystine		Absent	Present	Present
Lysine		Absent	–	Present
Arginine		Absent	Not known	Present
Responsible gene		SLC3A1	SLC7A9	
Band		2p21	19q13.1	
Population affected		Mediterranean Spanish persons, 40%	Libyan Jews	
Amino acid transport system localization in proximal converted tubule		Segment 3 ($S_3 > S_1$, S_2)	Segment 1 & 2 (S_1, $S_2 > S_3$)	

- Type A, mutation of both alleles of *SLC3A1*: Heterozygotes show a normal amino acid urinary pattern.
- Type B, mutation of both alleles of *SLC7A9*: Heterozygotes usually show an increase of cystine and dibasic amino acid urinary excretion.
- Type AB, cystinuria caused by 1 mutation in *SLC3A1* and 1 mutation in *SLC7A9*: Mixed-type cystinuria may be caused by the interaction of 2 distinct mutant genes, and the protein encoded by the 19q gene directly interacts with rBAT in the S3 segment of the proximal tubule.

For practical purposes at present extensive genetic sub classification of cystinuria seems unimportant in the short-term, but may facilitate future molecular or gene therapy. The determination of cystine concentration in urine will confirm a diagnosis and guide the intensity of future management. Although a significant amount of research has been conducted in this field, many questions remained unanswered. Why 55% of cystinurics develop stones? Are there other nongenteic factors/genes/transporters involved in the process?

5. Diagnosis

An accurate and early diagnosis of cystinuria is important in the long-term management of patients. All patients should have a baseline renal function and blood pressure recorded. Homozygous cystinuria is characterized by lifelong, recurrent stone disease that is difficult to manage, both surgically and medically. More than 50% of asymptomatic homozygotes develop kidney stones with 75% of these patients presenting with bilateral calculi [20].

The clinical symptoms of cystine stone disease are identical to that of other metabolic causes of renal calculi. A high index of suspicion should be held if the first stones are formed in the first 2 decades of life, in early recurrent stone disease, in patients with a family history of stone disease, and those with recurrent crystalluria.

5.1. Urinalysis

Microscopic examination of the urine may show hexagonal crystals that are pathognomonic of cystinuria. Cystine is one of the sulfur-containing amino acids; the urine may have the characteristic odour of rotten eggs. This may be particularly pronounced in the bladder urine drained following laser fragmentation of ureteric calculi.

The sodium-nitroprusside test is a rapid qualitative determination of cystine concentration that is no longer in routine clinical use. Cyanide breaks the di-sulphide bond of cystine liberating cysteine which then binds nitroprusside, causing a purple hue in 2-10 minutes [21]. A false-positive result may occur in individuals with homocystinuria or acetonuria, and in people taking sulfa containing drugs, ampicillin, or N-acetylcysteine. Fanconi syndrome causes a false-positive test secondary to generalized aminoaciduria. We feel that this test is an excellent cheap screening procedure for classical cystinuria. A positive cyanide-nitroprusside test should however be followed by ion-exchange chromatographic quantitative analysis of a 24-hour collected urine sample (Table 2).

Twenty-four–hour urine collection for other metabolic abnormalities will indicate the presence of hypercalciuria, hypocitraturia, and hyperuricosuria which may help to define a subgroup of patients at risk of failure of medical therapy due to the formation of noncystine or mixed calculi [22].

UriDynamics, a small company in Indianapolis, has developed a new test strip called StoneGuard II (http://www.uridynamics.com/). Currently, nitrazine paper and standard pH dipsticks have no clear colour differentiations in the 6–7.5 pH range. The StoneGuard II strip includes an additional colour block at a pH level of 7.5. The colours produced are yellow-orange (pH level of 5), yellow-green (pH level of 6), green-yellow (pH level of 6.5), light green (pH level of 7), green with blue cast (pH level of 7.5), and greenish blue (pH level of 8). No interference from common medications, nutritional supplements, or blood has been observed. It also has a pad to measure specific gravity over a range of 1.000–1.030.

Recently, Daudon et al. measured the cystine crystal volume (Vcys) from the early-morning urine to predict stone recurrence. They observed an average Vcys of 8173 μ^3/mm^3 in patients with recurrent cystine stone formation. In contrast, those who did not form stones had an average Vcys of 233 μ^3/mm^3. The absence of cystine crystals or a Vcys of less than 3000 μ^3/mm^3 was associated with the absence of cystine stone formation. The measurement of Vcys is helpful in assessing the effect of any treatment schedule. Daudon et al. reported an average Vcys of 12,000 μ^3/mm^3 in untreated patients, 2600 μ^3/mm^3 associated with conservative therapy, 1141 μ^3/mm^3 in patients with high fluid intake receiving mercaptopropionyl-glycine therapy, and 791 μ^3/mm^3 in patients with high fluid intake receiving penicillamine therapy [23].

Assessments of cystine excretion or solubility in the presence of cystine-binding thiol drugs are

difficult. Coe et al. have developed an assay for determining cystine capacity, a measure of the ability of urine either to take up additional cystine from a preformed solid phase (undersaturation, or positive cystine capacity) or to give it up to the solid phase (supersaturation, or negative cystine capacity) [24]. Cystine capacity can be used to monitor the response to the drug therapy and can help the clinician to prescribe minimal effective dose [25].

5.2. Stone analysis

Cystine stones are pale yellow and usually uniform in colour. Electron microscopic and x-ray diffraction crystallography may be useful in identifying stone components and specific spatial relationships of stone components. Pure cystine stones are observed in 60–80% of cases, sampling error may be high if only parts of calculi are examined rather than the complete stone.

Rough and smooth subtypes of cystine calculi have been identified by electron microscopic evaluation. Smooth calculi have an irregular, interlacing crystal structure, making them more resistant to fragmentation than the more homogenous hexagonal crystal structure of the rough subtype [26].

5.3. Imaging studies

An accurate initial diagnosis of renal colic is most readily made by helical CT scan, without intravenous contrast. Cystine stones have a homogeneous or ground-glass appearance on plain radiographs and although radio-opaque due to the presence of sulphur atoms, are often less dense than calcium-containing stones. Renal ultrasonography should provide the mainstay for follow up of cystine stone recurrence being firstly more economical than CT scan for monitoring the growth of renal calculi, and secondly reducing total radiation exposure. Cystinurics presenting in childhood with life long recurrence risk would otherwise accumulate large radiation doses over a lifetime.

6. Medical management

The cornerstone of cystine stone prevention is hydration and urinary alkalinization. If this conservative therapy fails drugs, such as D-penicillamine, alpha- mercaptopropionylglycine (MPG), and captopril may be added instigated. There is no current therapy that reverses the underlying derangement of dibasic amino acid transport.

6.1. Diet

Diets low in methionine are unpalatable and have demonstrated minimal benefit. In contrast, reduced salt intake (sodium intake 150 mmol/day) can decrease cystine excretion by as much as 156 mg/day (650 µmol/day) [27]. A reduction in salt intake to less than 2g/day has been recommended [28].

6.2. Hydration

The most important cystine stone-prevention technique is hyperdiuresis to decrease urinary cystine concentration. A homozygous cystinuric patient excretes between 600 and 1400 mg of cystine per day. At a pH of 7.0 the solubility of cystine is 250–300 mg/L. Simple maths indicate that a urine output of 5 Litres per day would be adequate to allow cystine clearance in solution for the majority of homozygous cystinurics; and indeed hydration alone can prevent stone recurrence in up to a third of patients. The goals of hydration therapy are urine volumes in excess of 3 L/d. This goal may require ingesting 4–4.5 L of water per day to allow for insensible loss. A suggested regimen would to drink 240 mL of water every hour during the day and 480 mL before bed, and at least once during the night [7,29]. Lindell et al. reported a marked rise in the incidence of stone formation when urinary cystine concentration was in excess of 700 µmol/l (170 mg/l)[30].

Alkalizing drinks rich in bicarbonate and low in sodium (1500 mg HCO3/L, maximum 500 mg sodium/L), and citrus juices may be of benefit. The success of hydration may be monitored by the patient by recording the specific gravity of their urine using Nitrazine dipsticks, with a goal of achieving a value less than 1.010 [5].

6.3. pH Balance

As already described the solubility of cystine is greater with higher pH. Urine of pH greater than 7.5 may encourage dissolution of formed calculi; however, urine pH of more than 7.5 can lead to the formation of calcium phosphate calculi. Ideally urine pH should be monitored to maintain a pH of 7.0–7.5 for optimum stone prevention.

Historically sodium bicarbonate was the first line alkalinising agent, however the sodium load may actually increase the amount of cystine excreted. Concerns have been expressed about increased risk of hypertension following long-term sodium bicarbonate therapy, and some patients will not tolerate the gaseous side effects of the drug.

The first line alkalinising agent is now potassium citrate. A typical adult dose is 60–80 mEq/d divided into 3–4 doses (15–20 mL/d). Optimal dose will be achieved by titration to achieve a urine pH within the target range of 7.0–7.5. Caution should be taken in prescribing large doses of potassium citrate in renal impairment [10,31].

6.4. *Drug therapy*

If hydration and alkalinisation fail to prevent cystine stone recurrence the next step in the treatment algorithm for cystinuria should be the introduction of chelation or antiurolithic therapy to decrease the urinary concentration below 300 mg/l [29].

Thiol compounds combine chemically with cystine to form a soluble disulfide complex that prevents stone formation and may even dissolve existing stones. D-Penicillamine is a first-generation chelating agent that in combination with cysteine is 50 times more soluble than cystine. The effect of the drug is dose-dependent; increasing dose by 250-mg/d decreases the urinary cystine level by 75–100 mg/d. Doses of 1–2 g/d are effective in reducing the urinary cystine level to 200 mg/g of creatinine.

Adverse reactions are common, approximately 50%; therefore, routine use is limited. Adverse effects include rash, arthralgia, leukopenia, gastrointestinal intolerance, and nephritic syndrome and should indicate treatment cessation. Long-term therapy may lead to vitamin B-6 (pyridoxine) deficiency; thus, vitamin B-6 supplementation (50 mg/d) is needed. Patients on D-penicillamine therapy should undergo regular monitoring of white blood cell count (including differentials), haemoglobin and platelet levels and urinalysis for proteinuria [32,33].

Alpha-mercaptopropionylglycine is a second-generation chelating agent with a chemical structure and mechanism of action similar to that of D-penicillamine. The usual dose is 10–15 mg/kg/d orally. Alpha-MPG has a 30% higher dissolution capacity for cystine than penicillamine. The mechanism of action is similar to that of D-penicillamine. Alpha-MPG is probably better tolerated than D-penicillamine with fewer patients discontinuing therapy due to side effects [34].

Captopril, a thiol first-generation ACE inhibitor, will form a thiol-cysteine mixed disulfide, 200 times more soluble than cystine. At a dose of 75–100 mg captopril may be used in patients who fail to respond to standard treatment, and to treat concomitant hypertension in cystinuric patients [35].

Bucillamine (Rimatil) is a third-generation dithiol compound, available only in Japan and South Korea. *In vitro* incubation of L-cystine with bucillamine and tiopronin dissolves a substantially greater amount of L-cystine than incubation with tiopronin alone. Bucillamine in the treatment of rheumatoid arthritis showed a low toxicity profile than penicillamine; therefore, it may be well tolerated by cystinuric patients. Data to support its use in the West is not available [36,37].

Tiopronin is an active cystine reducing agent that undergoes thiol-disulfide exchange to form tiopronin-cysteine disulfide. Akin to penicillamine-cysteine this is more water-soluble than cystine and is readily excreted. At a dose of 750 mg/d in three divided doses a chelating effect is seen within 4 hours. With a side effect profile similar to D-penicillamine caution is required in the initial weeks of prescription; both agents should be avoided in pregnancy [38].

7. Urological intervention

Large calculi that are associated with pain or infection and small obstructing or symptomatic stones require surgical intervention. Smaller, asymptomatic stones may be monitored as part of an active medical surveillance programme with close ultrasonographic follow-up. The establishment of a specialist metabolic stone clinic will facilitate follow-up, improve compliance with therapy and may also reduce surgical intervention rate [39,40].

Surgical options for treating cystine stones are no different to those that would be considered for the treatment of other types of urinary calculi.

7.1. *Extracorporeal shockwave lithotripsy*

Extracorporeal shockwave lithotripsy (ESWL) is an effective treatment for cystine stones, although overall stone-free rates are lower compared with rates for stones of other composition. Their hardness and homogenous amino acid composition, means most cystine stones require 2-3 times the usual number of shocks to adequately fragment the stone. Multiple treatments are often necessary. An upper limit of 1.5 cm diameter for upper ureteral or renal cystine calculi is proposed. Oral thiol therapy may produce cystine calculi that are more fragile because cystine is replaced by apatite in approximately 30% of cases, rendering these stones more ESWL sensitive [41,42].

7.2. *Retrograde endoscopic lithotripsy and extraction*

A retrograde, ureteroscopic approach is suitable for the majority of mid-to-distal ureteral cystine calculi

when using high-energy lithotripsy modalities such as holmium:YAG laser or pneumatic shock devices (e.g., Lithoclast). Smaller proximal ureteral calculi and small renal calculi are suitable for laser fragmentation following flexible ureteroscopic visualisation.

7.3. Percutaneous nephrolithotomy

Percutaneous nephrolithotomy was considered the gold standard for cystine renal calculi larger than 1–1.5 cm in diameter and for ESWL resistant stones. With the advances in flexible ureteroscopic design, and high energy laser lithotripsy PCNL may be reserved for larger calculi or complex stones. Having established percutaneous access ultrasonic lithotripsy readily fragments most cystine stones, although re-treatment rates are high; approximately 50% compared with 15% for other calculi. Stone-free rates following planned multiple treatments range from 40–86%; recurrence rates are high at 50–70% with 5-year follow-up despite postoperative medical management [43,44].

A large cystine stone burden, such as full staghorn calculi, may require multimodal therapy to achieve better stone-free rates. For example, initial PCNL delivered ultrasonic lithotripsy followed by ESWL and then repeat PCNL or flexible nephroscopy and laser lithotripsy, to complete stone clearance.

7.4. Percutaneous nephrostomy for chemical dissolution

Prior to the advent of minimally invasive surgical techniques direct irrigation of renal calculi with chemodissolution agents through a percutaneous nephrostomy tube was successful in treating a limited number of patients. Acetylcysteine creates soluble disulfide complexes with cystine, similar to the action of D-penicillamine. A solution containing 60 mL of a 20% solution of N-acetylcysteine and 300 mEq of sodium bicarbonate per litre of saline was recommended. Treatment could take weeks or months, and given these extended treatment times, relatively low success rates, and the advent of new surgical techniques, this is rarely used today [45,46].

7.5. Open surgery

With the success of percutaneous nephrolithotomy, ESWL, and endoscopic retrograde techniques, open surgery is contra-indicated as first-line therapy for cystine calculi anywhere in the kidneys or ureter.

8. Follow-up strategy

Effectiveness of the therapy should be monitored by determination of urinary pH and by measurement of 24-hours urinary cystine excretion. Follow-up clinic visits should be frequent but in patients with severe disease review should be done every 3 months with ultrasound imaging. Stone forming cystinuric patients are at risk for renal loss depending on the duration of follow-up and medical therapy, as many as 70% of patients may have renal insufficiency and end-stage renal disease may occur in <5% [47]. A 5-year stone recurrence rate of 73% after surgical intervention and 0.84 stone events per patient-year are to be expected; the probability of a recurrence-free survival at 1- and 5-year follow-up is 0.73 and 0.27, respectively. [44,48]. Active management in compliant patients with cystinuria decreases the incidence of surgical intervention [39,40]. The encouragement of compliance with prescribed medical treatment is essential for cystinuric patients.

9. The future

Because penicillamine and MPG have side effects, there is a need to expand and improve treatment options. Dimercaptosuccinic acid in vitro is an effective inhibitor of cystine precipitation but has not been tested in clinical trials [49]. Despite impressive molecular advancements in the description of cystine transport this does not appear to offer any new treatment modalities in the short term. Recently knockout mice for both cystinuria type I and cystinuria non type I have been developed and appear suitable for the study of the pathophysiology as well as for the evaluation of therapeutic and metaphylactic approaches for cystinuria [50,51]. Whether these models will play a role in the future is presently unclear. A rapid, non-invasive test strip for urinary cystine has been developed by the Keck Graduate Institute Team (Alameda, CA) working with BioCatalytics (http://www.kgi.edu/research/projects.shtml).

10. Summary

Cystinuria is a challenging and rewarding condition to treat requiring a range of medical and surgical strategies in co-operation between radiologist, nephrologist and urologist. The high recurrence rate of stone formation along with the early age of first stone formation necessitates long and close
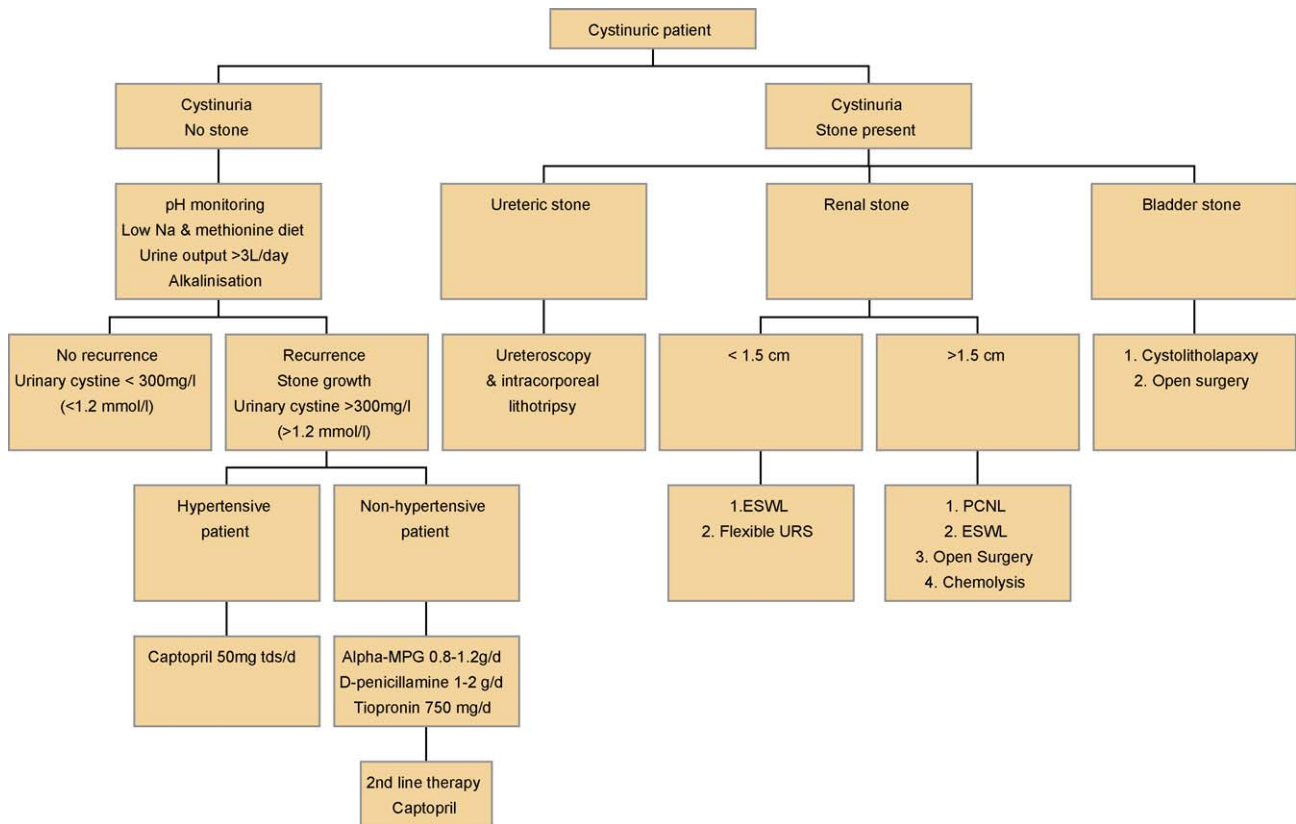
Fig. 1 – Algorithm for management of cystinuric patients. ESWL: extracorporeal shock wave lithotripsy, PCNL: percutaneous nephrolithotomy, URS: ureterorenoscopy.

follow-up. Treatment should aim to reduce the number of recurrent stone events in a patient's lifetime, preserve maximal renal function and limit radiation exposure. We propose a logical clinical management plan (Fig. 1) for managing a patient with cystinuria.

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CME questions

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1. Feature of cystinuria is
   A. An autosomal dominant defect in reabsorptive transport of cystine and the dibasic amino acids.
   B. Defective gene located on chromosome 11.
   C. The process of cystine uptake is activated by the SLC3A1 and SLC7A9 gene products.
   D. In normal individuals 1.4% of filtered cystine is lost in the urine.

2. Excretion of cystine
   A. Normal subjects excrete more than 30 mg/day (0.13 mmol/day).
   B. Homozygous patients excrete >400 mg/day (1.7 mmol/day).
   C. Type I and III heterozygotes excrete >200 mg/day (0.8 mmol/day).
   D. Type II heterozygous patients excrete in excess of 600–1400 mg/day (2.5–5.8 mmol/day).

3. Cystine calculi
   A. Are more likely to contain calcium in stones from homozygotes than heterozygotes.
   B. Are radio-opaque due to the presence of calcium.
   C. Show up clearly on computerised tomography (CT) scanning.
   D. Are soft and easily fragmented by ESWL.

4. On examination of the urine of patients with cystinuria
   A. Typical star-box shape crystals may be seen under microscopy.
   B. Nitroprusside may not be useful.
   C. The sodium-nitroprusside test causes a purple hue in 30 minutes.
   D. Quantitative urinalysis may be helpful in establishing a diagnosis of heterozygous versus homozygous cystinuria.

5. In the medical treatment of cystinuria
   A. Maintenance of an acidic pH is the mainstay of therapy.
   B. Hydration therapy should encourage a fluid intake of 4–4.5 pints per day.
   C. Urine pH of more than 7.5 can cause a predisposition to the formation of calcium oxalate stone.
   D. To dissolve calculi pH should be maintained over 6.5.

6. Drug therapy in cystinuria
   A. Penicillamine combines with cystine to form disulfide complex which is more soluble than cystine.
   B. The prevalence rate of adverse reaction is approximately 15%.
   C. Long-term therapy may lead to vitamin B12 deficiency.
   D. Alpha-MPG has poor dissolution capacity for cystine than penicillamine.