

## Cystine stones

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### GUIDELINES

No recommendations possible based on Level I or II evidence

### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

#### Diagnosis

- Cystine stones are diagnosed by stone analysis supported by the presence of cystine crystals or abnormally large quantities of cystine in the urine.

#### Treatment

- Stone growth and recurrences in cystinuria can be prevented by drinking sufficient fluid to increase urine volume to at least 3 L/day.
- Thiol drugs and orally active urinary alkalinisers are valuable adjuncts to high fluid intake.

### BACKGROUND

Cystine stones occur in subjects carrying two autosomal mutant alleles resulting in excessive excretion of cystine, ornithine, arginine and lysine – hence the condition cystinuria.

About 1:15–25 000 NSW neonates have been found to have cystinuria,<sup>1</sup> with a gene frequency in Australia calculated to be about 1:4000 individuals.<sup>2,3</sup> Since these studies were published, the mutant alleles have been identified and possibly there have been changes in Australian genetic demographics. There are three clinical subtypes. Type I heterozygotes excrete normal amounts of cystine, types II and III heterozygotes have higher than normal amounts but less than in the homozygote stone formers. Mixtures, e.g. type I/III, can occur. Type I/I 'classical cystinuria' is due to mutations in the SCL3A1 gene on chromosome 2. Homozygotes usually have two different mutations of the SCL3A1 gene.

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Mutations in the SCL 7A9 gene on chromosome 9 are associated with non-type I disease. The specific gene frequencies in the Australian population have not been reported. For simplicity, in these guidelines, patients who have two alleles with mutations of any of the genes will be referred to as 'homozygotes'.

### SEARCH STRATEGY

#### Diagnosis

**Databases searched:** Medline (1966 to June Week 2, 2004) – MeSH terms and text words for identifying cystine stones were combined with MeSH terms and text words for identifying diagnostic studies.

**Date of searches:** 23 July 2004.

#### Prevention

**Databases searched:** Medline (1966 to June Week 1, 2004) – MeSH terms and text words for identifying cystine stones were combined with MeSH terms and text words for interventions, and then combined with (i) the Cochrane search for randomized controlled trials (RCTs); and (ii) MeSH terms and text words for identifying meta-analyses and systematic reviews.

**Date of searches:** 23 July 2004.

### WHAT IS THE EVIDENCE?

No RCTs are available which address this issue.

There are no published levels of evidence for epidemiology. Levels of evidence for diagnosis depend on a suitable gold standard, for which none exists in cystine stone disease. There are no published RCTs to evaluate therapies in cystine stone disease. It is thus not possible to produce guidelines for cystine stone disease based on Level I and II evidence. The literature cited for therapy refers strictly to those reporting stone growth or recurrence in adult cystinurics, not those reporting effects on urinary cystine or cystine crystal formation.

## LEVEL III AND IV EVIDENCE

### Diagnosis

#### Clinical

Homozygous cystinurics experience stone episodes which usually commence in the first two decades of life, but may first occur at any age. Smith and Wilcken<sup>2</sup> found in Australia that 62% of cystinurics had a stone episode by 25 years of age – consistent with general international experience. Accordingly, recurrent stone disease of childhood onset is of value in suggesting cystinuria; however, onset in adulthood does not exclude this disease. As cystine stones occur in patients with two mutant alleles, the stone disease is effectively an autosomal recessive trait; hence siblings are sometimes also affected. However, many other forms of stone disease are familial, so this is not sufficiently characteristic to be diagnostic.

#### Radiological

The radiological appearance, though suggestive, is not diagnostic. Often bilateral, the stones are usually radiologically opaque but less so than calcium stones and sometimes they are radiolucent. They may have a uniform 'ground glass' appearance, and can grow to fill the pelvicalyceal system as a 'staghorn' calculus.

#### Urinary cystine crystals

The presence of hexagonal flat plate crystals in the urine is diagnostic of cystinuria, but has limited sensitivity as this depends on urine concentration, pH and temperature. They are therefore frequently absent, especially in dilute urine, hence this has a reported sensitivity of less than 30%.

#### Urinary cystine

Normal individuals excrete less than 100 mg/day (<0.42 mmol/24 h), <50 mg/g creatinine (<15 mmol/mmol creatinine) of cystine depending on the method of analysis and population studied.

Homozygous (I/I, II/II, III/III) stone-forming cystinurics excrete amounts around 5–10 times normal. Types II and III heterozygotes have intermediate excretion rates, with type II excreting less (2–3 times normal) than type III (3–4 times normal). Type I heterozygotes excrete normal amounts.

There are a variety of methods to detect cystine in the urine. The cyanide-nitroprusside reaction gives a colourimetric method for determining the presence of cystine in urine and is useful as a screening test particularly for homozygotes, although with modification most heterozygotes with abnormal cystine excretion will be also detected.<sup>4,5</sup>

High performance liquid chromatography (HPLC) is a more sensitive, specific and quantitative method for measuring cystine and other amino acids in the urine.<sup>5-7</sup>

For accurate diagnosis and quantification, HPLC is thus recommended.

Both HPLC and ion exchange chromatography can be used to assess free cystine excretion in the presence of thiol-cysteine disulphides produced by reaction with thiol drugs.<sup>8</sup> The usefulness of doing so has not been demonstrated to the extent that this could be justified in usual practice.

#### Genetic testing

Although the mutations in the SLC 3A1 and SLC 7A9 genes have been characterized in several populations,<sup>9-12</sup> genetic testing has as yet little place in the clinical care of cystinuric patients since phenotype is more important than genotype.<sup>13</sup>

Heterozygotes of types II and III can be detected by urine analysis. In the future, however, SLC 3A1 mutation analysis may be valuable, for instance, in detecting heterozygosity of type I in a prospective parent intending mating with a homozygous cystinuric, where 50% of children would be expected to have homozygous cystinuria.

#### Prevention of stone recurrence

##### Increased fluid intake

For over 50 years of studies, it has been known that the solubility of cystine in urine is greater than in water or buffered solutions, with crystals forming at pH 5–7 with concentration around 250–550 mg/L.<sup>14,15</sup> Since homozygotes often excrete >1000 mg/day, it can be calculated that urine excretion of >3–4 L/day is necessary to prevent stone formation. Increased fluid intake has thus been a cornerstone of treatment for over 50 years. Particular attention should be paid to nocturnal supersaturation.<sup>14</sup>

Dent *et al.*<sup>16</sup> attempted to assess the efficacy of large volumes of urine on cystinurics, reporting on 18 patients followed from 1945 to 1960, five of whom also were given sodium bicarbonate (one changed to potassium bicarbonate because of hypertension). In 12 of the 18 patients, stones either dissolved or the patients remained stone-free. They suggested that poor fluid intake had occurred in the other five patients.

Increased fluid intake is thus recommended, but has not been subjected to randomized clinical trial in cystinuria.

##### Alkalinization of urine

The suitability of cystine in urine increases with pH, but only significantly as pH exceeds 7. It has been reported that solubility is only slightly greater at pH 6 than at the isoelectric point of 3.76, increases by 50% at pH 7.5 and 1400% at pH 9. Solubility in urine is about 300 g/L at pH 7.2, and around 1000 mg/L at pH 8 (reviewed by Singer and Das<sup>17</sup>). The first stone dissolution by alkalinization of the urine was reported in 1924, and alkalinization of the urine has been mainstream treatment for over 50 years, though the degree of difficulty in maintaining pH above 7.2 is

acknowledged. Fjellstedt *et al.*<sup>18</sup> compared potassium citrate and sodium bicarbonate in 14 patients with homozygous cystinuria. In a 2-week cross-over study, both were equally effective as urinary alkalinisers, with a medium pH of 7.25 on sodium bicarbonate and 7.10 on potassium citrate ( $P = \text{ns}$ ).

Alkalinization of the urine is thus recommended as an adjunct to high fluid intake, recognizing the difficulty with long-term compliance.

### Thiol drugs

The cystine molecule is very insoluble, but reacts with drugs exposing a sulfhydryl group (-S-H) to form a thiol-cysteine-mixed disulphide that is much more soluble than cystine. A variety of such agents have been used in treating cystinuria. Of these, the only agent available for this indication on the Pharmaceutical Benefits Scheme is penicillamine.

Penicillamine, developed as a chelating agent for heavy metal toxicity, forms a penicillamine-cysteine complex which is approximately 50 times more soluble than cystine at pH 7.5 (reviewed by Singer and Das<sup>17</sup>). It was introduced as a treatment for cystinuria in 1963. Over the next few years, there were many small series (typical of the era) published demonstrating reduction in cystine excretion, cystine stone dissolution and reduction in stone recurrence in cystinuria not controlled by oral fluids and alkalinisers.

In these series, a very high incidence of side-effects was also reported. There are a variety of allergic reactions including rashes, arthralgia, nephrotic syndrome (membranous glomerulonephritis) and haematological (anaemia, neutropaenia, thrombocytopenia) reactions which usually occur early in the course of treatment. With usual daily dosage of 500–1000 mg, gastrointestinal side-effects (anorexia, nausea, vomiting, abdominal pain, diarrhoea) are common and with long-term use peripheral neuropathy can occur. It is estimated that about 50% of patients will cease penicillamine because of side-effects.

Halperin *et al.*<sup>19</sup> retrospectively reviewed stone episodes in terms of lithotomies and renal colic episodes per 100 patient-years in 56 cystinurics treated in north-eastern USA in the period of 1940–1978. From these the 35 patients who had had surgical lithotomy were designated as 'severe'. Thirty-two had received penicillamine at some stage. Stone episodes had occurred at a rate of 13.2/100 patient-years (total 14.7 patient-years) in patients while being treated with penicillamine, compared with 25.1/100 patient-years (total 210.5 patient-years) in those receiving only fluids or fluids/alkali ( $P < 0.05$ ). They concluded that the penicillamine treatment programmes significantly reduced episodes of renal colic. Acute drug sensitivity occurred in over 40%, proteinuria in 34% of treated patients; hence penicillamine should be reserved for selected high-risk patients.

Accordingly, patients given penicillamine must be monitored closely and continuously, restricting its use to only the most difficult cases, and even then often for limited periods.

**Alpha-mercaptopropionylglycine** ( $\alpha$ -MPG, tiopronin, Thiola®) is a sulfhydryl compound introduced as an alter-

native to penicillamine in cystinurics intolerant to that agent. It is reputed to have similar though fewer side-effects compared with penicillamine.

Miano *et al.*<sup>20</sup> reported on  $\alpha$ -MPG treatment combined with encouragement to drink and urinary alkalinisers in 42 patients over the period 1972–1977. Achieved urine volumes ranged between 930 and 3500 mL during  $\alpha$ -MPG treatment. Urine pH was not reported, but the aim was to keep it above 7.0. Complete or patient stone dissolution occurred in 79% of 19 patients with stones, and stone formation in only one of 27 patients without associated urinary infection. Interestingly, they observed no allergic side-effects, only one case of gastric intolerance and one of taste loss.

Koide *et al.*<sup>21</sup> reported on 35 patients treated with  $\alpha$ -MPG since 1970 for stone dissolution and/or prevention of recurrence. In 27 patients treated for more than 1 year, they reported significant stone dissolution in seven and new stone formation prevented in 23. Dosage was 300–1800 mg daily. All received 2–6 g of sodium bicarbonate daily and were encouraged to increase oral fluid intake. Systemic reactions such as fever, skin rash, oedema or general malaise occurred soon after starting therapy in 10 of 35 patients.

Pak *et al.*<sup>22</sup> reported a multicentre trial recommended by Food and Drug Administration to determine the safety and efficacy of  $\alpha$ -MPG in patients with known toxicity with penicillamine, and also to determine whether biochemical responses were similar to penicillamine.

The study was not designed to compare the effectiveness of  $\alpha$ -MPG to penicillamine nor to compare the side-effect profile. Sixty-six patients were enrolled, all of whom had had at least one stone episode in the 2 years before treatment with  $\alpha$ -MPG. All maintained their previous fluid and alkali intake. Of 49 patients who had previously taken D-penicillamine, six were intolerant of  $\alpha$ -MPG. The 43 remaining took  $\alpha$ -MPG for periods from 4 months to 3.7 years (mean 1.81 years), and the stone rate fell from  $8.5 \pm 22.3$  stones/patient-year during the 2 years before  $\alpha$ -MPG treatment, to  $3.7 \pm 13.2$  stones/patient-year ( $P < 0.001$ ). Cessation of stone formation was observed in 63%.

Of 17 patients who had not had D-penicillamine at any stage, 14 continued  $\alpha$ -MPG for more than 4 months. The new stone formation rate fell from  $5.3 \pm 13.0$  stones in the previous 2 years to  $1.83 \pm 1.29$  stones/patient-year on  $\alpha$ -MPG for periods from 4 months to 4 years ( $P < 0.001$ , chi-squared test). Cessation of stone formation was observed in 71%.

As with D-penicillamine, side-effects were common, being mainly gastrointestinal (anorexia, nausea, vomiting, abdominal pain) but also allergic reactions such as rash and proteinuria. These findings are consistent with other experiences of the drug, many reported in books or proceedings.

Lindell *et al.*<sup>8</sup> treated 31 patients with  $\alpha$ -MPG, documenting the fall in free urinary cystine by ion-exchange chromatography, keeping it to less than 1100 mol/L. All were encouraged to maintain high fluid intake and take sodium bicarbonate aiming at a urinary pH 7–8. Four of the 31 were intolerant of sodium bicarbonate. Thirteen of the 31 patients on  $\alpha$ -MPG were free of stone formation or

growth, and renal stone episodes fell from median 0.4 (0–3.0) in the year before  $\alpha$ -MPG, to median 0.09 (0–1.0) in the year on  $\alpha$ -MPG ( $P < 0.001$ , Wilcoxon's signed rank test). Urine volumes did not change appreciably. Interestingly, urinary free cystine levels had only a vague relationship to stone episodes per year, and no relationship to new stone formation.

Lindell *et al.*<sup>8</sup> noted that a paper by Linari *et al.*<sup>23</sup> found a similar rate of 0.21 episodes/year in 30 patients on  $\alpha$ -MPG, commenting that the much lower basic rate than in the Pak *et al.*<sup>22</sup> study was a probably outcome of patient selection.

Taken together, the Lindell *et al.*<sup>8</sup> and Pak *et al.*<sup>22</sup> studies both show a reduction in stone episode/formation by a factor of about 2–4 fold with the use of  $\alpha$ -MPG in patients with cystinuria already taking fluids and alkali but still forming stones.

Pak *et al.*<sup>22</sup> found that 5–9% of patients treated with  $\alpha$ -MPG having not been previously exposed to penicillamine were forced to discontinue because of adverse reactions; however, over 60% of patients reported side-effects, with a similar profile to those reported with penicillamine. Of the 31 patients treated with  $\alpha$ -MPG by Lindell *et al.*,<sup>8</sup> six (19%) withdrew, four with proteinuria and one with a lupus-like syndrome.

The conclusion of both, neither of whom volunteered drug company sponsorship, was that  $\alpha$ -MPG was more tolerable than penicillamine.

There have been no randomized comparisons of penicillamine and  $\alpha$ -MPG in patients with cystinuria.

Captopril, an angiotensin-converting enzyme inhibitor is also a thiol compound (D-3-mercapto-2-methylpropionyl-L-proline). It can thus form captopril-cysteine disulphide, which is 200 times more soluble than cystine. Sloan and Izzo<sup>24</sup> reported a fall in free urinary cystine in two patients on captopril, but did not report on stone formation. Cohen *et al.*<sup>25</sup> gave 150 mg daily to nine patients with cystinuric stones but were unable to show a statistically significant difference in rates of stone events.

### Combination therapy

Because of the wide variation in tolerance of high fluid intake, oral alkali administration and the thiols, mixed combination therapies are usually employed.

Barbey *et al.*<sup>26</sup> reported treatment outcomes in 27 adults with cystine stones, including 274 patient-years pre-referral (retrospective), and 312 patient-years post-referral (prospective) followed at the Necker Hospital for at least 1 year between 1963 and 1998. Treatments included high fluid intake to achieve a total urine volume of at least 3 L/day, sodium bicarbonate (22) or potassium citrate (5) and if these failed, penicillamine 600 mg–1200 mg, or  $\alpha$ -MPG 500 mg–1000 mg daily was added, at least half of the dose to be taken at bedtime. Three patients had 100–150 mg of captopril. Pre-referral stone episode rate was 0.93 episodes/patient-year, while on therapy this fell to 0.20 episodes/patient-year.

In attempting to analyse the most important factor, patients were divided into 15 successes (no urological pro-

cedure while on therapy) and 12 failures (requiring urological procedures while on therapy). Other than stone episodes/year and urological procedures/year, the only difference between the two groups was mean urine volume ( $3.15 \pm 0.65$  L vs  $2.45 \pm 0.65$  L,  $P < 0.006$ ). Urine pH was similar ( $7.6 \pm 0.6$ ,  $7.5 \pm 0.5$ ) and four successful and five unsuccessful patients were taking thiols. High fluid intake was regarded therefore as of the highest importance in treatment of cystinuria.

Chow and Strem<sup>27</sup> reviewed the Cleveland Clinic experience in 35 cystinurics followed for at least 6 months between 1983 and 1995. The regimen was high fluid intake, urinary alkalization with sodium bicarbonate, potassium citrate or balanced citrate aimed to keep urine pH greater than 7.5, and thiols including penicillamine 1000–200 mg or  $\alpha$ -MPG 800–1200 mg in divided doses. Failure or intolerance of these lead to the addition of captopril 150 g daily. Urine volumes reported in this series were only mean 2.07 L (range 0.76–4.38 L) per day. The relative effect of volume of diuresis was not analysed. The urine pH achieved was not reported or analysed.

Overall, with 'hydration and alkalization', the stone events rate was 1.6/patient/year. With alkalization plus thiols, the rate was 0.52, with alkalization plus captopril 0.71, and alkalization with thiols and captopril 0.54 episodes/patient-year. The outcome was 0.84 stone events/patient-year, which they felt was a realistic expectation in treating stone-forming cystinurics.

## SUMMARY OF THE EVIDENCE

There are no RCTs on this topic.

## WHAT DO THE OTHER GUIDELINES SAY?

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

## INTERNATIONAL GUIDELINES

No recommendation.

## IMPLEMENTATION AND AUDIT

Because of the multiple disciplines (primary care physicians, physicians, nephrologists and urologists), there is minimal possibility of implementing or auditing evidence-based cystine stone guidelines, if such guidelines could be produced.

## SUGGESTIONS FOR FUTURE RESEARCH

- 1 Non-toxic agents reducing cystine excretion may be developed.
- 2 Australian demography of the genetic causes requires study.

## CONFLICT OF INTEREST

Gavin Becker has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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## APPENDIX

## Characteristics of included studies

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments and results
Increased fluid intake								
Dent <i>et al.</i> <sup>16</sup>	18	Prospective cohort	London, UK	17 homozygote, 1 heterozygote, all stone formers	Efficacy of large volumes of urine on cystinurics	Nil	15 years	12/18 stones dissolved or patients remained stone-free
Alkalinization of urine								
Fjellstedt <i>et al.</i> <sup>18</sup>	14	Cross-over, prospective	Sweden	14 patients with homozygous cystinuria	2 weeks sodium bicarbonate, 2 weeks potassium citrate	Nil	2 weeks	Both equally effective Potassium citrate Medium pH 7.10 Sodium bicarbonate Medium pH 7.25
Penicillamine								
Halperin <i>et al.</i> <sup>19</sup>	56	Retrospective, reviewed stone episodes in terms of lithotomies and renal colic episodes per 100 patient-years	North-eastern USA	56 cystinurics	Penicillin Stone episodes 13.2/100 patient-years (total 14.7 patient-years)	Fluids or fluids/alkali Stone episodes 25.1/100 patient-years	1940-1978	Acute drug sensitivity (>40%); proteinuria (34%)
Alpha-mercaptopyropionylglycine								
Miano <i>et al.</i> <sup>20</sup>	42	Prospective cohort	Italy	42 patients	$\alpha$ -MPG combined with encouragement to drink and urinary alkalinisers	Nil	5 years: 1972-1977	Achieved urinary volume 930-3500 mL. Complete or patient stone dissolution occurred in 79% of 19 patients with stones and stone formation in 1 of 27 patients without associated urinary infection.
Koide <i>et al.</i> <sup>21</sup>	35	Retrospective cohort	Japan	35 patients	Treated with $\alpha$ -MPG since 1970; dosage 200-1800 mg/day. 2-6 g sodium bicarbonate daily and encouraged to increase oral fluid intake.	Nil	1970-1981	In 27 patient treated for >1 year, stone dissolution = 7, new stone formation prevented in 23, systemic reactions, skin rash, oedema, general malaise in 10/35.

## APPENDIX continued

Study ID (author, year)	n	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments and results
Pak <i>et al.</i> <sup>22</sup>	66	Multicentre FDA-recommended trial (not designed to compare effectiveness of $\alpha$ -MPG to penicillamine, not to compare side-effect profile)	Texas, USA	66 patients	Those with $\geq 1$ stone episode in 2 year before treatment with $\alpha$ -MPG.	Nil	1980–1986	43 took $\alpha$ -MPG for 4 months–3.7 years, stone rate fell from $8.5 \pm 22.3$ stones/patient-year during the 2 years before $\alpha$ -MPG treatment to $3.7 \pm 13.2$ stones/patient-year ( $P < 0.001$ ). Cessation of stone formation 63%. Of 17 who had not had D-penicillamine at any stage, 14 continued $\alpha$ -MPG for >4 months. New stone formation rate fell from $5.3 \pm 13.0$ stones in the previous 2 year to $1.83 \pm 1.259$ stones/patient-year on $\alpha$ -MPG for 4 months–4 years ( $P < 0.001$ ). Cessation of stone formation 71%. 13/31 $\alpha$ -MPG patients were free of stone formation or growth, renal stone episodes fell from median 0.4 (0–3.0) to 0.09 (0–1.0), $P < 0.001$ .
Lindell <i>et al.</i> <sup>8</sup>	31	Retrospective case cohort	Sweden	31 homozygous cystinurics	$\alpha$ -MPG, free urinary cystine	High fluid intake and sodium bicarbonate	1979–1955	
Captopril								
Cohen <i>et al.</i> <sup>25</sup>	9	Prospective case cohort		9 patients with a history of multiple cystine stones	50 mg captopril 3 times daily	High fluid intake and alkalinization therapy	1–3 years observation	Rate of new stone formation or stone growth fell from 0.7 to 2.0 events (mean 1.2) per patient-year for 1–3 years of observation to 0–3.0 (mean 1.03) per patient-year for 0.5–6 years, $P = 0.35$ .
Combination therapy								
Barbey <i>et al.</i> <sup>26</sup>	27	Retrospective and prospective	Necker hospital, France (1963–1998)	27 adults with cystine urolithiasis	Basic therapy included hyperdiuresis and alkalinization. Total urine volume $\geq 3$ L/day, sodium bicarbonate (22), potassium citrate (5) and if these failed penicillamine 600–1200 mg or $\alpha$ -MPG 500–1000 mg/day.			Pre-referral stone episode rate was 0.93 episodes/patient-year; therapy: 0.20 episodes/patient-year. $P < 0.001$
Chow <i>et al.</i> <sup>27</sup>	35	Retrospective	Cleveland clinic	35 cystinurics followed $\geq 6$ months (1983–1995) 16 patients with cystinuria	High fluid intake, sodium bicarbonate, potassium citrate or balanced citrate, thiols or captopril 150 mg/day.		7–141 months	Stone event rate (per patient per year): hydration and alkalinization 1.6; alkalinization + thiols 0.52; alkalinization + captopril 0.71; alkalinization + thiols + captopril 0.54. Overall 0.84.