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# Adverse events associated with currently used medical treatments for cystinuria and treatment goals: results from a series of 442 patients in France

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## Objective

To evaluate medical treatments, in terms of adverse events (AEs) and therapeutic goals, in a large series of patients with cystinuria.

## Patients and Methods

Data from 442 patients with cystinuria were recorded retrospectively. Crystalluria was studied in 89 patients. A mixed-effects logistic regression model was used to estimate how urine pH, specific gravity and cysteine-binding thiols (CBT) correlate with risk of cystine crystalluria.

## Results

Alkalinizing agents and CBT agents were given to 88.8% ( $n = 381$ ) and 55.3% ( $n = 238$ ) of patients, respectively. Gastrointestinal AEs were reported in 12.3%, 10.4% and 2.6% of patients treated with potassium bicarbonate, potassium citrate and sodium bicarbonate, respectively ( $P = 0.008$ ). The percentages of patients who experienced at least one AE with tiopronin (24.6%) and with D-penicillamine (29.5%) were similar ( $P = 0.45$ ). Increasing urine pH and decreasing urine specific gravity significantly reduced the risk of cystine

crystalluria, whereas D-penicillamine and tiopronin treatments did not reduce this risk (odds ratio [OR] 1 for  $\text{pH} \leq 6.5$ ; OR 0.52 [95% confidence interval {95% CI} 0.28–0.95] for  $7.0 < \text{pH} \leq 7.5$ ,  $P = 0.03$ ; OR 0.26 [95% CI 0.13–0.53] for  $7.5 < \text{pH} \leq 8.0$ ,  $P < 0.001$ ; OR 1 for specific gravity  $\leq 1.005$  OR 5.76 [95% CI 1.45–22.85] for  $1.006 \leq$  specific gravity  $\leq 1.010$ ,  $P = 0.01$ ; and OR 11.06 [95% CI 2.76–44.26] for  $1.011 \leq$  specific gravity  $\leq 1.014$ ,  $P < 0.001$ ). Increased urine pH significantly increased the risk of calcium phosphate crystalluria (OR 1 for  $\text{pH} \leq 6.5$ ; OR 6.09 [95% CI 2.15–17.25] for  $\text{pH} > 8.0$ ,  $P < 0.001$ ).

## Conclusion

Adverse events were frequent with D-penicillamine and tiopronin. Alkaline hyperdiuresis was well tolerated and reduced cystine crystalluria. Urine specific gravity  $\leq 1.005$  and urine  $\text{pH} > 7.5$ , while warning about calcium-phosphate crystallization, should be the goals of medical therapy.

## Keywords

cystinuria, D-penicillamine, potassium citrate, sodium bicarbonate, tiopronin

## Introduction

Cystinuria (OMIM 220100), a genetic defect of cystine tubular reabsorption, is responsible for 1% of nephrolithiasis cases in adults and between 8% and 10% of cases in children [1,2]. Cystinuria is caused by mutations in *SLC3A1* or *SLC7A9* genes, encoding, respectively, for the subunits rBAT and b0, +AT of an amino acid transporter B0 [3–6]. Because of the poor solubility of cystine at urine  $\text{pH} < 7$ , cystinuria results in stone formation. The rates of new stone formation and of urological procedures are significantly higher in patients with cystinuria than in other stone formers [7,8]. We recently reported a high prevalence (27%) of chronic kidney disease among adults with cystinuria and its association with severe damage to renal parenchyma [9]. This risk of renal impairment has also been reported by other authors [3,10], highlighting the need for adequate preventive medical treatment. As treatment is early and long-term, its safety and tolerability are key elements of its success.

Alkaline hyperdiuresis remains the cornerstone of preventive treatment. D-penicillamine and tiopronin, two cysteine-binding thiol (CBT) agents, produce cysteine complexes that are 50 times more soluble than cystine [1]. The efficacy of captopril, a third CBT agent, is questionable [1]. Tolerance of alkalinization has rarely been described [11,12]. Moreover, most authors recommend

tiopronin rather than D-penicillamine as it appears to be associated with a lower frequency of adverse events (AEs), although they have been reported at rates close to those of D-penicillamine [12–18]. Cystine crystalluria and cystine crystal volume are known to be associated with the risk of stone formation [19]. A recent study has confirmed the usefulness of crystalluria for the monitoring of patients with cystinuria [20]. Given the importance of preventive treatments, we conducted a multicentre retrospective study, including 442 people with cystinuria, to evaluate AEs associated with preventive treatments and to identify therapeutic targets, using cystine crystalluria as a surrogate marker of cystine stone formation [19].

## Patients and Methods

### Study Population

We contacted all nephrology, urology and paediatrics departments in France that were likely to manage kidney stones, asking physicians to complete a questionnaire in April 2010. A proven diagnosis of cystinuria based on stone analysis, crystalluria, urine cystine excretion, or sodium-cyanide-nitroprusside test [1] was the only inclusion criterion. The study received approval from the advisory committee on information processing research in the field of health (number 10.640bis).

## Data Collection

Data were retrospectively collected from the medical record between April 2010 and January 2012 by the physician in charge of the patient, via completion of a specific questionnaire designed for the study. Charts were systematically surveyed. The data collected included epidemiological and clinical characteristics, laboratory data, medical and surgical treatments and comorbidities. All medical data from the beginning of the medical history were included even if they were recorded before April 2010. The end of the study for each patient was the date the questionnaire was sent by the physician in charge of the patient.

Medical treatments were categorized as alkalinizing therapy (AT; alkalinizing beverage, potassium citrate, sodium bicarbonate, potassium bicarbonate and other ATs (a mix of trométamol, sodium citrate and potassium citrate, or a second mix of citric acid, potassium citrate and sodium citrate) or CBT agents (D-penicillamine, tiopronin or captopril). Patients could be treated concomitantly or successively with more than one AT and with more than one CBT agent; therefore, the number of ATs and CBT agents could be higher than the number of patients studied. We then excluded captopril from our analysis as its efficacy has not been proven [13,21]. AEs related to treatment were registered by the physician in charge of the patient and categorized according to the type of AE. In order not to miss an AE, all AEs without any definition restriction could be registered excepted for proteinuria (renal AE) which was defined according to 24-h urinary protein excretion (proteinuria  $\geq 0.3$  g/24 h) or protein/creatinine ratio on urinary spot sample (protein/creatinine ratio value  $\geq 30$  mg/mmol). Other types of AE registered were gastrointestinal (stomach or abdominal pain, diarrhoea, loss of taste, nausea, vomiting, gastrointestinal intolerance, abdominal discomfort, epigastralgia, oral ulcers, gingivitis, gastric ulceration), haematological (defined according to the normal values of each laboratory: thrombocytopenia, leukopenia, anaemia, eosinophilia, aplastic, methemoglobinaemia), cutaneous (urticaria, pruritus, rash, eczema, erythema, alopecia), pulmonary (dyspnoea), and other AEs (cramps, malaise, abnormalities in liver function tests, mouth soreness, fluorosis [bone and dental disorders caused by the ingestion of too much fluoride in drinking water]).

Crystalluria was studied [19,22] for patients followed at a single centre (Necker Hospital, Paris). Patients were asked to collect the first morning urine and were authorized to drink during the night as usual. Well-homogenized spot urine samples (released to the laboratory within 2 h of voiding) set in a Malassez cell were examined by light microscopy equipped with a polarized light device. The type of crystal was determined based on morphology, coupled with their polarizing features and urine pH. Urine pH and specific gravity were measured in those spot urine samples with

double zone pH paper (Duotest<sup>®</sup>, Macherey-Nagel, Düren, Germany) and test strips (Multistix<sup>®</sup>, Siemens Healthineers, Erlangen, Germany). Cystine crystal volume was determined using the formula:  $V_{cys} = 0.65 \times N \times L^2 \times T$ , where  $V_{cys}$  = cystine crystal volume,  $N$  = number of cystine crystals per  $\text{mm}^3$ ,  $L$  = average length of the crystals measured between two opposite angles and  $T$  = average thickness of the crystals. Cystine crystal volume was expressed as  $\mu\text{m}^3/\text{mm}^3$  of urine, including both isolated crystals and aggregate.

Cystine concentration was measured by ion-exchange chromatography using an amino acid analyser (JLC 500 Aminotac, JEOL Europe S.A, Croissy Sur Seine, France) in 24 h or in spot urine samples collected the same day as urine samples for crystalluria. The cystine concentrations are related to creatinine. Only free cystine was measured in patients treated with CBT as this assay can distinguish free cystine and cystine bound to CBT.

Stone composition was analysed by infra-red spectroscopy. Mixed stones were defined as cystine stones also containing  $\geq 10\%$  calcium phosphate and/or  $\geq 10\%$  calcium oxalate and/or presence of struvite. A 'pure' cystine stone was a calculus without any of the preceding criteria.

## Statistical Analyses

Data are presented as medians with minimum and maximum values, means  $\pm$  SD, and as percentages. For continuous data, means were compared with a *t*-test, ANOVA when more than two groups were studied, or Wilcoxon's test, as appropriate. For categorical data, percentages were compared with a chi-squared test or Fisher's exact test, as appropriate. A mixed-effects logistic regression model was fitted to study the association between urine pH, specific gravity, CBT, and the risk of cystine crystalluria for a given patient. Univariate and multivariate analyses including urine pH, specific gravity and CBT were performed. All estimated odds ratios were adjusted based on time between the date of diagnosis and the date of crystalluria as this was a longitudinal analysis. The same method was used to study the association between urine pH, specific gravity and the risk of having calcium phosphate crystalluria. The association between urinary cystine excretion and crystalluria was assessed with a linear mixed model. Patient was included as a random effect.

*P* values  $< 0.05$  were taken to indicate statistical significance. All analyses were performed with the R package (v3.2.4).

## Results

### Description of the Population

A total of 150 clinical departments were contacted, and the response rate was 31%. We collected data on 442 patients (220 males) from 47 clinical departments specializing in

urology ( $n = 8, 101$  patients), paediatrics ( $n = 16, 91$  patients), and nephrology ( $n = 23, 250$  patients). Demographic and clinical data on the patients are summarized in Table 1.

## Description of Medical Treatments and Adverse Events

Alkalinizing therapy and/or CBT were given at least once to 90.6% of patients: 1.87% were treated with CBT alone, 35.36% with AT alone, and 53.4% with both CBT and AT. Ninety-five patients (24.5%) treated with AT or CBT experienced at least one AE. AEs were attributed to CBT in 71.9% of cases and to AT in 28.1% of cases.

## Alkalinizing Therapy

An AT was given to 88.8% of patients ( $n = 381/429$ , No data Available (NA) = 13). Alkalinizing beverage, potassium citrate, sodium bicarbonate, potassium bicarbonate and other ATs were given to 55.7%, 51.2%, 41.4%, 17.3% and 11.4% of patients receiving AT, respectively. At last follow-up, patients were treated with none, one, two or three ATs in 14.9%, 51.1%, 30.7% and 3.3% of cases, respectively.

**Table 1** Demographic and clinical data.

Characteristic	
Symptomatic patients ( $N = 442$ ), %	91.0
Median (min.–max.) age at presentation ( $N = 357$ ), years	16.7 (0.3–72.1)
Male	16.5 (0.3–72.1)
Female	17.1 (0.3–72.1)
Median (min.–max.) age at diagnosis ( $N = 360$ ), years	18.5 (0.0–74.3)
Sex: male ( $N = 442$ ), %	49.8
Ethnicity ( $N = 381$ )	
White	74.3
Black African	0
Other	25.7
Median (min.–max.) age at last follow-up ( $N = 439$ ), years	32.5 (0.3–86.6)
Diagnostic tools (%) ( $N = 366$ )	
Stone analysis, %	57.7
Cystinuria assessment, %	28.5
Crystalluria, %	3
Sodium-cyanide-nitroprusside test, %	1.9
Several tests, %	8.9
Median (min.–max.) time from initial symptoms to last follow-up ( $N = 359$ ), years	15.8 (0.1–65.6)
Median (min.–max.) time from first to last medical visit ( $N = 440$ ), years	4.1 (0.0–41.5)
Median (min.–max.) delay from first symptoms to diagnosis ( $N = 300$ ), years	1.3 (0.0–45.7)
Median (min.–max.) delay from first symptoms to first urological intervention ( $N = 282$ ), years	0.5 (0.0–45.7)
Median (min.–max.) delay from first symptoms to first medical treatment ( $N = 276$ ), years	2.8 (0.0–45.7)
High blood pressure ( $N = 434$ ), %	21.4
Diabetes mellitus ( $N = 434$ ), %	3.8
Obesity ( $N = 425$ ), %	10.4
eGFR <60 mL/min/1.73 m <sup>2</sup> ( $N = 372$ ), %	23.4
≥1 urological intervention ( $N = 435$ ), %	81.8
≥1 surgical nephrotomy or ureterolithotomy ( $N = 429$ ), %	38.7
≥1 percutaneous nephrolithotomy or shock wave lithotripsy or ureteroscopy ( $N = 430$ ), %	72.8

eGFR, estimated GFR. Diagnosis of high blood pressure was retained if the patient was declared by the physician to have hypertension, irrespective of antihypertensive treatment. Diagnosis of obesity relied on a body mass index  $\geq 30$  kg/m<sup>2</sup> or a positive answer to the question regarding obesity. eGFR was calculated using the last available plasma creatinine and the Modification of Diet in Renal Disease v4 equation in patients aged > 16 years at the time of testing [46] and the Schwartz equation in patients aged < 16 years if body height was available [47]. Episodes of acute renal failure were excluded.

Thirty-five patients (9.3% of those treated with AT at any time [35/377, NA = 4]) experienced a total of 39 AEs: 33 patients had 36 gastrointestinal AEs and three patients experienced fluorosis.

Gastrointestinal AEs comprised abdominal discomfort, epigastralgia, abdominal pain, nausea, vomiting, diarrhoea, ulcers in mouth and gastric ulceration; they occurred mainly with potassium citrate and potassium bicarbonate (10.4% and 12.3% of patients treated, respectively) compared with 2.6% of patients treated with sodium bicarbonate ( $P = 0.008$ ).

Digestive AEs attributable to AT lead to treatment discontinuation (26/36, 72.2%), dose reduction (7/36, 19.4%) and no action (3/36, 8.3%). All digestive AEs resolved after these actions (NA for two AEs). Digestive AEs resulted in at least one treatment discontinuation in 6.4% (24/377) and at least one dose reduction in 1.9% of patients (7/377) treated with AT.

Finally, fluorosis (assigned to alkalinizing beverage) was reported in 0.8% of patients treated with AT ( $n = 3/377$ ).

## Cysteine-Binding Thiol Agents

In all, CBTs were given to 55.3% of patients ( $n = 238$ , NA = 12). D-penicillamine, tiopronin and captopril were prescribed

in 59.1% ( $n = 139$ , NA = 3), 55.9% ( $n = 133$ ) and 23.4% of patients ( $n = 55$ , NA = 3) treated with CBTs, respectively. The prescription of tiopronin in newly symptomatic patients significantly increased with time (Fig. 1). Patients were treated during their follow-up with one, two or three CBTs (D-penicillamine and/or tiopronin, and/or captopril) in 37.7% ( $n = 161$ ), 13.8% ( $n = 59$ ) and 3.5% ( $n = 15$ ) of cases, respectively (NA = 15). The mean  $\pm$ SD durations of treatment with tiopronin and D-penicillamine were  $4.9 \pm 5.4$  and  $8.1 \pm 9.5$  years, respectively (Table S1). Duration of treatment was significantly longer with D-penicillamine than with tiopronin in patients who had been treated with only one of each treatment (Table S2). In contrast to D-penicillamine, tiopronin was not used before the 1980s. (Figure 1).

In the D-penicillamine group, 41/139 patients (29.5% of the treated patients at any time) reported an AE, and in the tiopronin group, the reporting rate was 24.6% (32/130 patients treated at any time, three NA;  $P = 0.45$  [Fig. 2A]). The treatment duration was similar for D-penicillamine and tiopronin in patients treated only with one of each treatment and who experienced an AE (Table S2).

In the D-penicillamine group, the majority of patients reported one AE (32/41, 78.1%), seven patients reported two AEs (7/41, 17.1%) and two patients reported three AEs (2/41, 4.9%). The distribution of AEs was as follows: proteinuria (16/52, 30.8%), gastrointestinal AEs (13/52, 25.0%), cutaneous AEs (12/52, 23.1%), haematological AEs (5/52, 9.6%), pulmonary AEs (2/52, 3.8%) and one other AE (4/52, 7.7%): cramps, malaise or abnormalities in liver function tests. Four patients treated with D-penicillamine who had proteinuria underwent a renal biopsy; no membranous glomerulonephritis was observed.

In the tiopronin group, the majority of patients reported one AE (26/32, 81.2%), five reported two AEs (5/32, 15.6%) and one patient reported four AEs (1/32, 3.1%). The distribution of AEs was as follows: proteinuria (10/40, 25.0%), gastrointestinal AEs (10/40, 25.0%), cutaneous AEs (13/40, 32.5%), haematological AEs (6/40, 15.0%) and one case of mouth soreness (1/40, 2.5%).

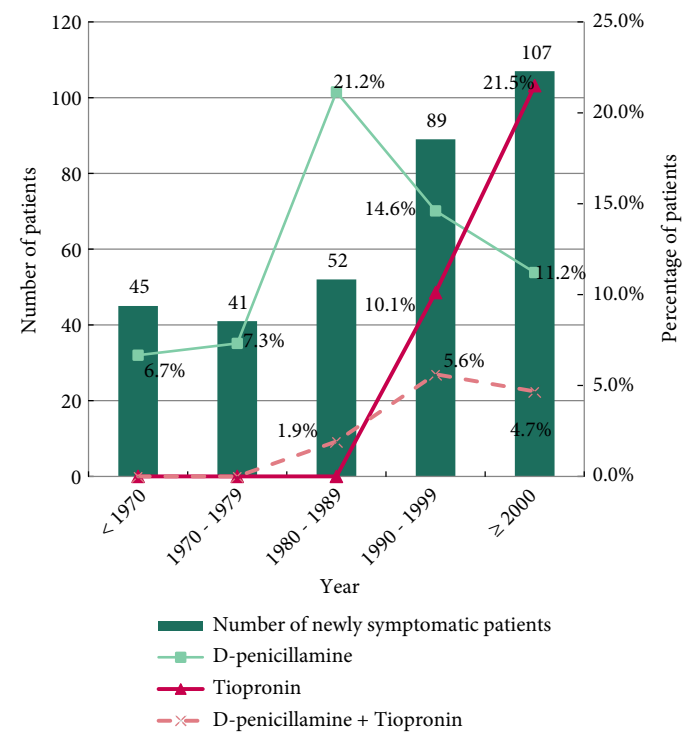
The duration of treatment with D-penicillamine was shorter in patients who had an AE as compared to patients without AEs, whereas there was no difference in treatment duration in patients with and without AEs treated with tiopronin (Table S1). Doses of D-penicillamine or of tiopronin were similar in patients with or without AEs (Table S1). Doses and treatment durations according to each type of AE are described in Table S3.

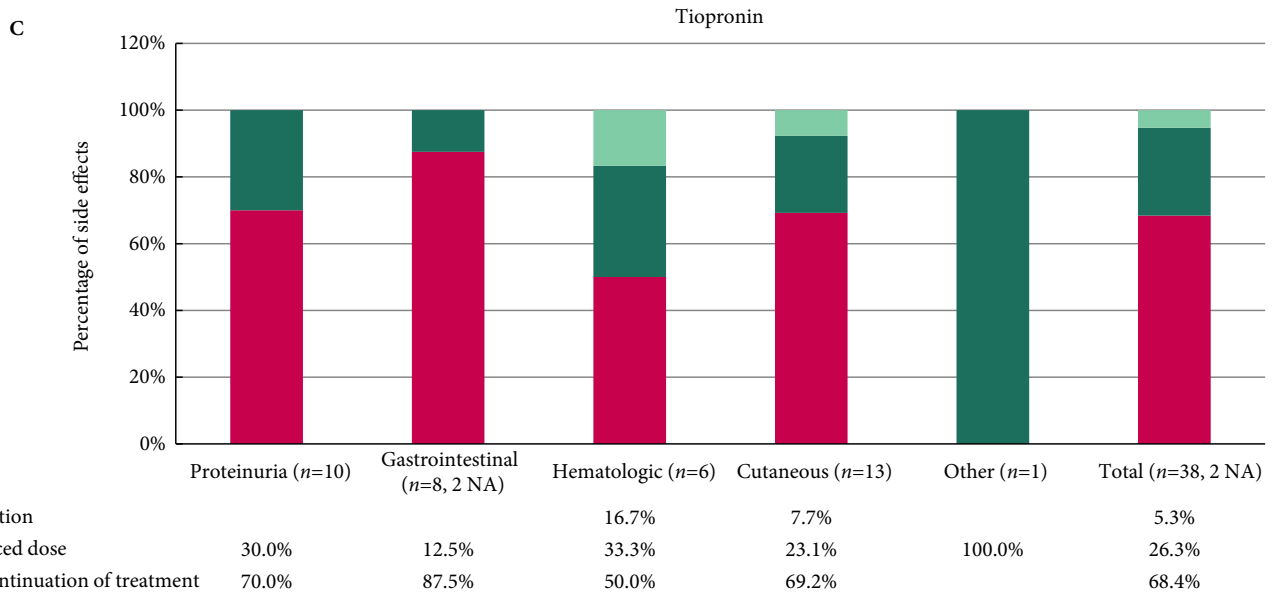
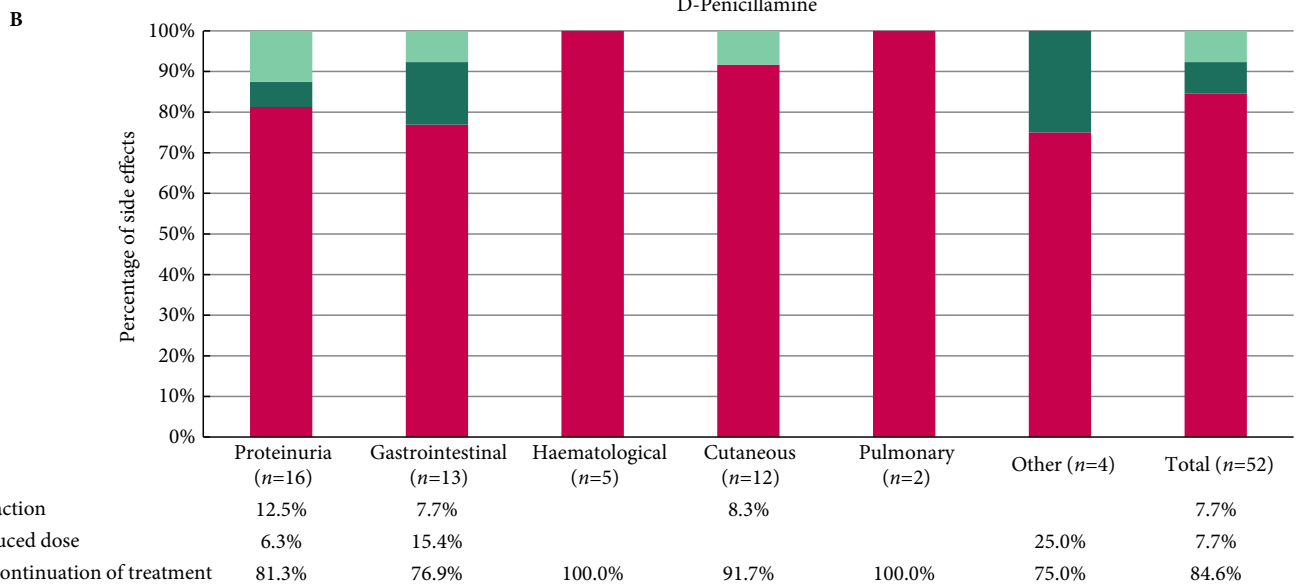
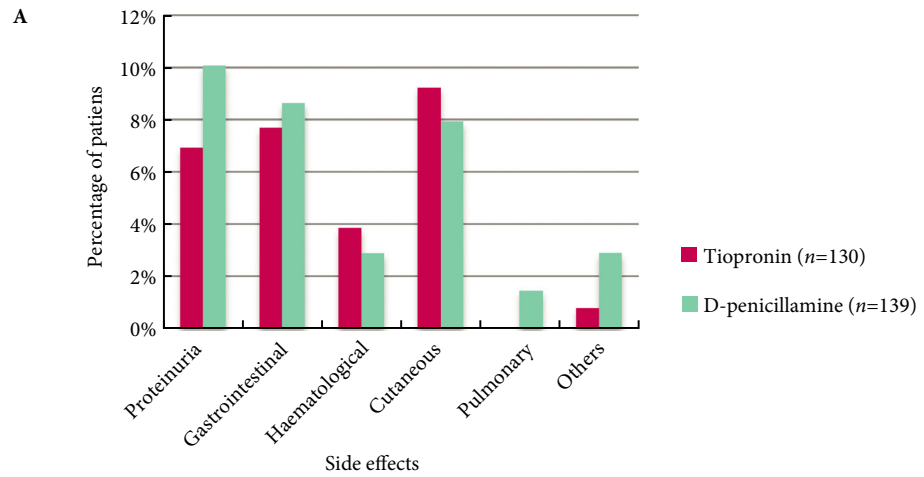
The AEs associated with D-penicillamine resulted in treatment discontinuation in 84.6% of cases vs 68.4% for those associated with tiopronin ( $P = 0.12$ ; Figs 2B and C). AEs associated with tiopronin more frequently resulted

(26.3%) in a dose reduction than those associated with D-penicillamine (7.7%;  $P = 0.03$ ).

Finally, AEs resulted in at least one treatment discontinuation in 25.9% of patients treated with D-penicillamine ( $n = 36/139$ ) and in 18.5% of those treated with tiopronin ( $n = 24/130$ ;  $P = 0.19$ ), whereas 2.2% of patients treated with D-penicillamine ( $n = 3/139$ ) and 4.7% of patients treated with tiopronin ( $n = 6/129$ , NA = 1) had at least one dose reduction attributable to AEs ( $P = 0.32$ ).

After discontinuation of treatment, outcome was favourable in 88.4% of cases for D-penicillamine and in 96.2% of cases for tiopronin ( $P = 0.61$ ; Tables S4 and S5).





**Fig. 2** Adverse events (AEs) associated with cysteine-binding thiols (CBTs). **(A)** Percentage of patients treated with tiopronin and D-penicillamine who experienced AEs. AEs recorded were proteinuria, and digestive (stomach or abdominal pain, diarrhoea, loss of taste, nausea, vomiting, gastrointestinal intolerance, oral ulcers, gingivitis), haematological (thrombocytopenia, eosinophilia, leukopenia, aplastic, anaemia, methemoglobinaemia), cutaneous (urticaria, pruritus, rash, eczema, erythema, alopecia), pulmonary (dyspnoea) and other AEs (cramps, malaise, abnormalities in liver function tests, mouth soreness). AEs were studied in patients treated with D-penicillamine (139 patients) and with tiopronin (130 patients); no AE data were available for three patients treated with tiopronin). Ten percent (10.1%,  $n = 14$ ), 8.6% ( $n = 12$ ), 7.9% ( $n = 11$ ), 2.9% ( $n = 4$ ), 1.4% ( $n = 2$ ) and 2.9% ( $n = 4$ ) of patients treated with D-penicillamine had proteinuria, digestive AEs, cutaneous AEs, haematological AEs, pulmonary AEs and other AEs. Six percent (6.9%,  $n = 9$ ), 7.7% ( $n = 10$ ), 9.2% ( $n = 12$ ), 3.8% ( $n = 5$ ) and 0.8% ( $n = 1$ ) of patients treated with tiopronin had proteinuria, digestive AEs, cutaneous AEs, haematological AEs, and other AEs. The differences in percent of patients with AEs of tiopronin and D-penicillamine were not statistically significant when type of AE was considered ( $P = 0.48$  for proteinuria,  $P = 0.66$  for digestive AEs,  $P = 0.87$  for cutaneous AEs,  $P = 0.74$  for haematological AEs,  $P = 0.50$  for pulmonary AEs,  $P = 0.37$  for the other AEs). **(B)** Consequences of AEs on continuation of D-penicillamine therapy. **(C)** Consequences of AEs on continuation of tiopronin.

Forty-six patients were treated with D-penicillamine and with tiopronin at different times during follow-up. Among them, nine patients (19.6%) experienced an AE with D-penicillamine only, eight patients (17.4%) experienced an AE with tiopronin only and seven patients (15.2%) had AEs with both treatments. Type of AE and outcomes for these seven patients are described in Table S6. Only one patient had the same type of AE (proteinuria) with both treatments.

### Effect of the Preventive Medical Treatments on Crystalluria

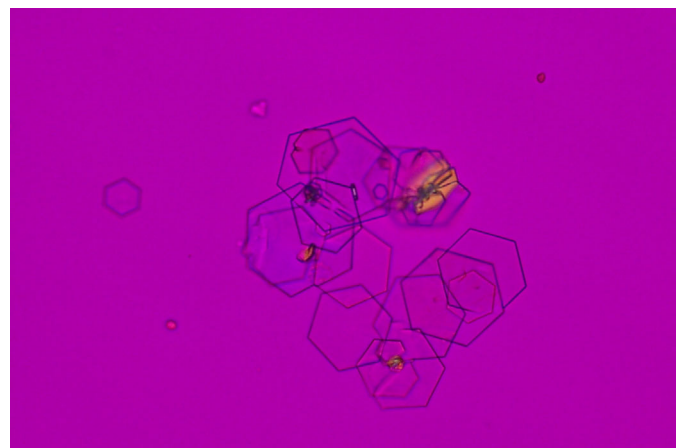
Because cystine crystalluria [19] has previously been shown to be strongly associated with stone formation among patients with cystinuria, we studied crystalluria in a subgroup of 89 patients with demographic data similar to those of the entire population (Table S7) to evaluate the effect of the different preventive medical treatments on this surrogate marker. The median (range; mean  $\pm$  SD) number of crystalluria examinations per patient was 4.0 (1–65;  $8.1 \pm 10.9$ ). Considering the period from first to last crystalluria examination (median [range; mean  $\pm$  SD] 4.5 [0–25.4;  $6.3 \pm 6.8$ ] years), the median (range; mean  $\pm$  SD) number of crystalluria studies per patient per year was 1.4 (0.2–7.8;  $1.8 \pm 1.6$ ). Among the 722 samples analysed, 269 (37.3%) were positive for cystine crystalluria (Fig. 3).

Increasing urine pH and decreasing urine specific gravity significantly reduced the risk of positive cystine crystalluria for a given patient, whereas treatment with CBT, including D-penicillamine or tiopronin (captopril was excluded), did not reduce this risk regardless of the dose as shown by univariate (Table S8) and multivariate analyses (Table 2).

The estimated probability of having cystine crystalluria for a given patient according to urine pH, urine specific gravity, and dose of CBT are plotted in Fig. 4A–C. Notably, if urine specific gravity is  $< 1.005$ , crystalluria is positive for cystine in  $< 20\%$  of cases, regardless of pH (Figure 4D).

A cystine crystal volume  $\geq 3000 \mu\text{m}^3/\text{mm}^3$  has been reported to be predictive of stone recurrence [19]. Increasing urine pH and decreasing urine specific gravity significantly reduced the

**Fig. 3** Cystine crystals ( $\times 200$ ). Cystine crystals are hexagonal crystals of great size (30–70  $\mu\text{m}$ ) with lamellar aspect and parallel edges.



**Table 2** Multivariate analyses of associations between urine pH, urine specific gravity and cysteine-binding thiol (D-penicillamine and/or tiopronin) with the risk that a given patient will have cystine crystalluria.

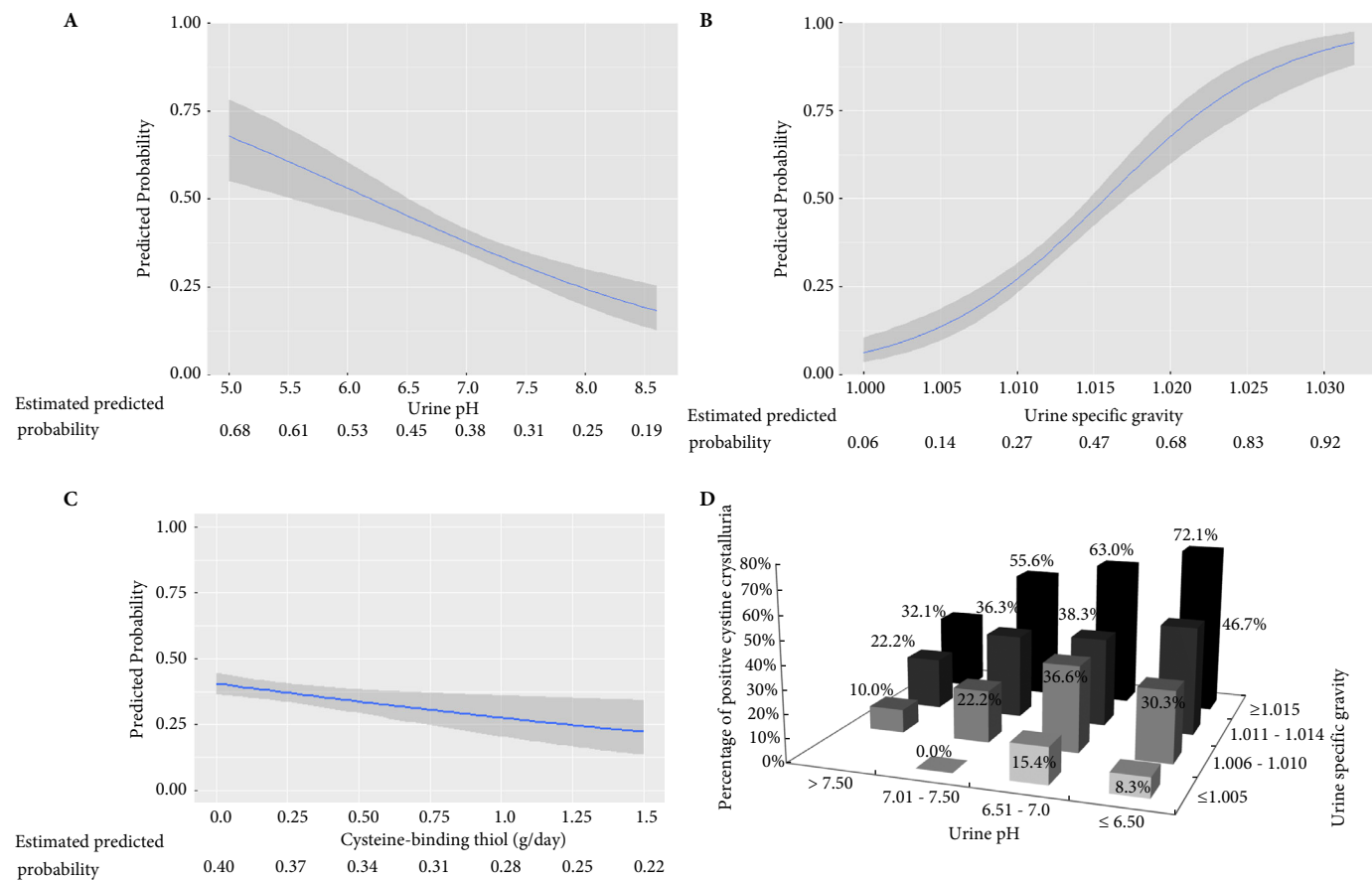
	OR (95% CI)	P
<b>pH</b>		
pH $\leq 6.5$	1	
$6.5 < \text{pH} \leq 7.0$	0.77 (0.44–1.35)	0.35
$7.0 < \text{pH} \leq 7.5$	0.52 (0.28–0.95)	0.03
$7.5 < \text{pH} \leq 8.0$	0.26 (0.13–0.53)	$< 0.001$
pH $> 8.0$	0.11 (0.04–0.31)	$< 0.001$
<b>Specific gravity</b>		
$\leq 1.005$	1	
1.006–1.010	5.76 (1.45–22.85)	0.01
1.011–1.014	11.06 (2.76–44.26)	$< 0.001$
$\geq 1.015$	26.93 (6.65–109.02)	$< 0.001$
<b>CBT, g/day</b>	0.63 (0.28–1.41)	0.26

CBT, cysteine-binding thiol; OR, odds ratio. OR values were adjusted based on the delay between date of diagnosis and date of crystalluria measurement.

risk of having a cystine crystal volume  $\geq 3000 \mu\text{m}^3/\text{mm}^3$  for a given patient ( $n = 67$  patients with cystine crystalluria had a cystine crystal volume  $\geq 3000 \mu\text{m}^3/\text{mm}^3$ ), whereas treatment with CBT (D-penicillamine or tiopronin) did not reduce this risk, regardless of the dose, as shown by univariate (Table S9) and multivariate analyses (Table 3). We did not find any



**Fig. 4** Study of cystine crystalluria. Estimated predicted probability of cystine crystalluria as a function of (A) urine pH, (B) urine specific gravity, and (C) D-penicillamine or tiopronin treatment dose. The estimated risk of cystine crystalluria for a given patient increased when the pH decreased and when the specific gravity increased. Dose is expressed in g/day. (D) Percentage of positive cystine crystalluria as function of urine pH and urine specific gravity. Crystalluria with a urine pH >7.5 and a urine specific gravity ≤1.005 was excluded from this analysis owing to lack of data for this urine pH and this urine specific gravity.



cystine crystal volume  $\geq 3000 \mu\text{m}^3/\text{mm}^3$  when urine specific gravity was  $\leq 1.005$ .

Moreover, we did not find any association between urinary cystine excretion and cystine crystalluria (Table S10, Figure S1).

Because it is known that increasing urine pH induces phosphocalcic precipitation [23], we studied the risk of calcium phosphate crystalluria. Fifty patients (56.2%) had at least one positive calcium phosphate crystalluria. Among the 722 samples analysed, 205 (28%) were positive for calcium phosphate crystals. As expected, increasing urine pH significantly increased the risk of positive calcium phosphate crystalluria for a given patient (Table S11, Fig. 5A) and this was confirmed by multivariate analysis (Table 4). However, there was no difference in terms of risk of calcium phosphate crystalluria when pH categories > pH 7 were compared (Table 4). The estimated risks of calcium phosphate crystalluria for a given patient according to urine pH and specific gravity are plotted in Figs 5A and 5B.

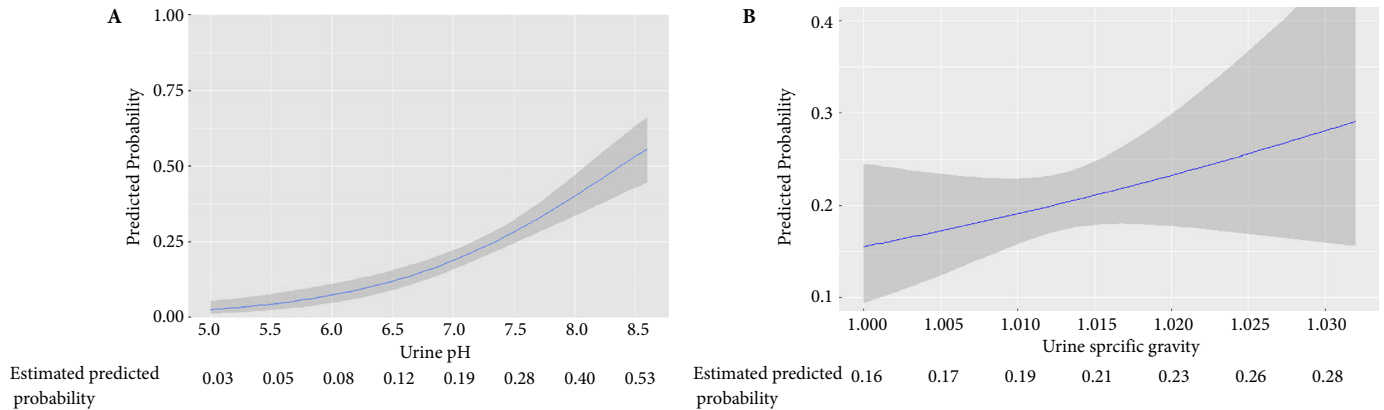
**Table 3** Multivariate analyses of associations between urine pH, urine specific gravity and cysteine-binding thiol (D-penicillamine and/or tiopronin) and the risk of a given patient having cystine crystal volume  $\geq 3000 \mu\text{m}^3/\text{mm}^3$ .

	OR (95% CI)	P
<b>pH</b>		
pH $\leq 6.5$	1	
6.5 < pH $\leq 7.0$	0.73 (0.35–1.51)	0.39
7.0 < pH $\leq 7.5$	0.41 (0.17–1.01)	0.05
7.5 < pH $\leq 8.0$	0.07 (0.01–0.32)	<0.001
pH > 8.0	0.14 (0.03–0.72)	0.02
<b>Specific gravity</b>		
$\leq 1.010$	1	
1.011–1.014	4.76 (1.48–15.33)	0.009
$\geq 1.015$	15.85 (5.13–48.92)	<0.001
<b>CBT, g/day</b>	0.99 (0.36–2.73)	0.99

CBT, cysteine-binding thiol; OR, odds ratio.

Stone compositions were known for 385 calculi from 224 patients (Table 5). Thirty-three patients (14.7%) passed at least one stone containing  $\geq 10\%$  calcium phosphate. Forty

**Fig. 5** Study of calcium phosphate crystalluria. Estimated predicted probability of a calcium phosphate crystalluria as a function of (A) urine pH and (B) urine specific gravity.



**Table 4** Multivariate analyses of associations between urine pH, urine specific gravity and the risk of a given patient having calcium phosphate crystalluria.

	OR (95% CI)	P
<b>pH</b>		
pH ≤6.5	1	
6.5 < pH ≤ 7.0	4.11 (2.02–8.39)	<0.001
7.0 < pH ≤ 7.5	8.15 (3.74–17.74)	<0.001
7.5 < pH ≤ 8.0	7.36 (3.22–16.82)	<0.001
pH > 8.0	6.09 (2.15–17.25)	<0.001
<b>Specific gravity</b>		
≤1.005	1	
1.006–1.010	1.35 (0.32–5.66)	0.68
1.011–1.014	1.91 (0.46–7.91)	0.37
≥1.015	2.51 (0.61–10.33)	0.20

OR, odds ratio. OR values were adjusted based on the delay between date of diagnosis and date of crystalluria measurement.

patients followed at one centre (Necker Hospital, Paris) underwent at least one crystalluria examination (360 crystalluria tested) and one stone analysis (69 calculi analysed). The presence of a stone containing ≥10% calcium phosphate was associated with a higher frequency of calcium phosphate crystalluria: four patients had at least one stone containing ≥10% calcium phosphate and all of these patients had > 30% crystalluria positive for calcium phosphate, whereas among the remaining 36 patients with only pure cystine calculi, only 33% had > 30% crystalluria positive for calcium phosphate ( $P = 0.02$ ).

## Discussion

To the best of our knowledge, this is the first reported evaluation of efficacy and safety of cystinuria medical treatments. Medical treatment of this rare disease is currently based on a stepwise strategy using in the first instance alkaline hyperdiuresis, with further addition of a CBT if necessary [13].

**Table 5** Stone analyses.

<b>Mixed stones (N = 385 stones), %</b>	
Pure cystine	89.1 (n = 343)
≥1 other component	10.9 (n = 42)
≥10% calcium phosphate and ≥10% calcium oxalate	0.8 (n = 3)
≥10% calcium phosphate and <10% calcium oxalate	8.3 (n = 32)
≥10% calcium phosphate and NA for calcium oxalate	0.3 (n = 1)
<10% calcium phosphate and ≥10% calcium oxalate	1.6 (n = 6)
<b>Patients with mixed stones (N = 224 patients), %</b>	
Pure cystine calculi only	83.5 (n = 187)
≥1 mixed stone	16.5 (n = 37)
≥10% calcium phosphate and ≥10% calcium oxalate	1.3 (n = 3)
≥10% calcium phosphate and <10% calcium oxalate	12.1 (n = 27)
≥10% calcium phosphate and NA for calcium oxalate	1.3 (n = 3)
<10% calcium phosphate and ≥10% calcium oxalate	1.8 (n = 4)

NA, No data Available. Mixed stones were defined as cystine stones also containing ≥10% calcium phosphate and/or ≥10% calcium oxalate and/or presence of struvite. A 'pure' cystine stone was defined as a calculus without any of the preceding criteria. We found 11 calculi with ≥30% calcium phosphate. Five of which contained ≥70% calcium phosphate. No patient had a stone containing struvite.

In the present study, 89% of patients were treated with AT, similar to the percentages reported for other studies (87% to 100% of patients) [24,25]. AT was well tolerated with < 10% of patients reporting one AE. Notably, we found that sodium bicarbonate was better tolerated than either potassium citrate or potassium bicarbonate. As urine cystine excretion increases moderately along with sodium intake [11,26–31] in studies involving only a small number of patients, patients with cystinuria are usually advised to avoid excessive sodium consumption [1,32]. The high prevalence (28.6%) of high blood pressure among adults with cystinuria [9] and the existence of mixed calculi containing calcium also support sodium restriction [32,33]. Potassium bicarbonate or potassium citrate is recommended to achieve alkalization without a sodium load; however, the effect of sodium on cystine transport has been questioned in *in vitro* studies [34]. Moreover, to our knowledge, no prospective study has evaluated the effect of

sodium bicarbonate vs AT without sodium on cystine course. It is commonly accepted that the benefit of AT including sodium is higher than the risk of a sodium load. Unfortunately, sodium excretion was not available to corroborate that our patients on sodium bicarbonate had a higher urine cystine excretion. We can speculate that to limit sodium intake while increasing treatment adherence, a combination of ATs was often prescribed, probably explaining why more than one-third of patients in our study were being treated with more than one AT.

In all, CBTs were prescribed for 55.3% of our patients. The percentage of patients treated with CBTs varies in other smaller series from 23% to 90% [10,12,21,24,25,35–38], but in series with a large number of patients, the percentage is frequently > 50% [10,12,35] except in one study (34%) [21]. More patients experienced at least one AE during D-penicillamine in comparison with tiopronin, but the difference was not significant. As tiopronin-related AEs tended to result in less treatment discontinuation in our patients and induced more dose reduction than did AEs associated with D-penicillamine, we hypothesize that the overall safety of tiopronin may be slightly better than that of D-penicillamine. In smaller series of patients with cystinuria, the frequency of AEs attributable to tiopronin and D-penicillamine varied from 5% to 70% [10,14–16] and from 18% to 84% [10,12,14,17,18,35,39], respectively. It should be noted that the majority of AEs resolved after the discontinuation of the treatment involved. As no prospective randomized trial has compared these treatments, our results in a larger series of patients enhance the information available regarding their tolerability.

Among patients who were treated with tiopronin and D-penicillamine, ~15% experienced an AE with both drugs but, in most cases, the AE was not the same, ruling out a high frequency of real cross-reactivity.

Given the discrepancy in frequency of AEs between AT and CBT reported in the present study, we also sought to identify therapeutic targets to better manage these treatments. To do this, we chose to analyse cystine crystalluria, which has been shown to be a reliable surrogate marker of stone formation [19]. We chose not to use urological interventions as a marker for cystine stone recurrence as several urological procedures could be necessary to treat only one calculus and a urological intervention can occur for a long time after stone formation. Moreover, the activity of cystinuria in terms of incident stone formation is very difficult to assess accurately retrospectively owing to unnoticed spontaneous stone passage and symptom-free stones only detected by routine ultrasonography. Finally, we did not evaluate our therapeutic targets according to daily urine cystine excretion as there is no significant relationship between the 24-h excretion of cystine and the formation of new stones during tiopronin

treatment [40]. Importantly, we did not find any association between urinary cystine excretion and cystine crystalluria which was to be expected as cystine excretion in 24-h urine samples gives no information about peak concentration. Urinary flow, urinary cystine excretion and urinary cystine concentration have diurnal variations and the peak concentrations of cystine in 6-h samples are ~90% higher than the corresponding concentrations in 24-h urine samples [41]. Moreover, the solubility of cystine and cystine crystalluria depends also on pH which is not taken into account with the dosage of cystine excretion.

We would like to emphasize that crystalluria is not a routine analysis available everywhere so that the aim of the present study was not to recommend the use of crystalluria for the monitoring of the preventive medical treatment in patients with cystinuria, but to determine goals for urine pH and specific gravity, which can be easily self-monitored or measured in a clinical laboratory based on the probability of having cystine crystalluria according to these different parameters.

Although crystalluria data were available for only 89 patients, this is the largest group of patients with cystinuria for which these data have been collected. This subgroup of patients had the same epidemiological characteristics as those of the entire population. We showed that a decrease in urine specific gravity significantly reduced the risk of cystine crystalluria. We also demonstrated that the probability of cystine crystalluria increased as urine specific gravity increased from 1.005 to 1.010. Furthermore, if specific gravity was < 1.005, cystine crystalluria was positive in < 20% of cases, regardless of urine pH. Although urine volume was higher in patients with cystinuria who had discontinued stone formation [24], the exact target of urine specific gravity had never been clearly defined. Importantly, our results show for the first time that the target of specific gravity should be 1.005 rather than 1.010, as previously proposed by others [1]. If fluid intake is well distributed over the 24-h period, there is an almost linear relationship between morning urine specific gravity and 24-h urine volume, and a morning specific gravity of 1.005 corresponds to a 3 L/24 h diuresis [42]. Specific gravity can be self-monitored by patients with cystinuria to be sure to achieve the required target.

Urine dilution is rarely well distributed and sufficient, therefore, urine alkalinization is required to increase cystine solubility [43]. The effect of urine alkalinization on the course of cystine stone formation has been poorly studied [43,44]. In the present study, increasing urine pH significantly decreased the risk of cystine crystalluria (OR 1 for pH ≤ 6.5, OR 0.26 [95% CI 0.13–0.53] for 7.5 < pH ≤ 8.0) and the risk of having a cystine crystal volume ≥ 3000 μm<sup>3</sup>/mm<sup>3</sup>, which is associated with stone recurrence [19]. It is currently recommended that patients maintain urine pH between 7.5

and 8.5 [32]; however, we would like to emphasize that the predicted probability of calcium phosphate crystalluria significantly increased with pH to reach a plateau above pH 7. Furthermore, 15% of our patients passed at least one calculus containing between 10% and 95% of calcium phosphate, and these patients were more likely to have calcium phosphate crystalluria. These results underscore the risk of alkalinization [23]. Another recent study reported a high frequency of non-cystine stones mostly comprising calcium phosphate in patients with cystinuria [45]. Consequently, in order not to substitute one disease with another, we suggest that stones should be analysed systematically in order to detect calculi containing calcium phosphate, and urine pH should be self-monitored to avoid insufficient but also over-alkalinization.

Although it has been reported that CBTs reduce stone activity in patients with insufficient alkaline hyperdiuresis [35,40], the efficacy of CBTs in patients with cystinuria has never been evaluated in a prospective randomized trial (effect of alkaline hyperdiuresis plus placebo vs alkaline hyperdiuresis plus CBT) to confirm the usefulness of CBT. In the present series, we did not find any significant association between the use of CBT and cystine crystalluria, even at low urine pH, which challenges the efficacy of CBT in patients with cystinuria. Although it has previously been reported that CBTs lower cystine crystal volume [19] in a smaller study, urine pH, urine specific gravity and CBTs were not included in a multivariate analysis.

A prospective study is warranted to confirm our targeting urine pH and specific gravity and to evaluate CBT efficacy based on stone activity using clinical and radiological assessment.

We acknowledge that the present study has limitations. There may have been selection bias as not all the centres in France responded to our questionnaire. However, this bias may have overestimated the proportion of patients with AEs, as the clinicians with no safety issues may have been more likely not to respond. Because of the retrospective design, we were faced with heterogeneous follow-up times and some data were missing. Adherence to CBT could not be studied and we do not know if CBT prescription was correlated with disease severity. We reported the duration of treatment until an AE was declared by the physician which may have been longer than the time to when the AE began. Unfortunately, as we reported only few AEs, we were unable to compare the delay in AE occurrence between D-penicillamine and tiopronin.

The present study also has several strengths. It included a large number of patients with prolonged follow-up, which enabled us to describe and analyse the outcome of medical treatments over time, their safety profile and the risk of cystine crystalluria for a given patient using a mixed-effects

logistic regression model, an analysis never previously performed.

In conclusion, D-penicillamine and tiopronin both induce AEs in approximately one-quarter of patients, with no clear effect on cystine crystalluria. In contrast, alkaline hyperdiuresis is well tolerated and efficiently reduces occurrence of cystine crystalluria, which is a strong predictor of cystine stone recurrence [19]. Based on cystine crystalluria analyses, we suggest for the first time that the target of urine specific gravity should be  $\leq 1.005$  and we confirm that patients should maintain urine pH  $> 7.5$ , while emphasizing the risk of calcium phosphate crystallization.

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## Conflict of Interest

None declared.

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**Abbreviations:** OR, odds ratio; CBT, cysteine-binding thiol; AE, adverse event; AT, alkalinizing therapy; NA, No data Available.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Fig. S1.** Association between urinary cystine excretion and cystine crystalluria.

**Table S1.** Treatment dose and treatment duration of D-penicillamine and tiopronin in all patients and in patients who had or not an adverse effect.

**Table S2.** Comparison of treatment duration with D-penicillamine and tiopronin in all patients and in patients who had an adverse event.

**Table S3.** Dose and treatment duration according to the type of adverse event.

**Table S4.** Medical management of adverse events induced by D-penicillamine and its consequences.

**Table S5.** Medical management of adverse events induced by Tiopronin and its consequences.

**Table S6.** Adverse events and outcomes in patients who had adverse events with both tiopronin and D-penicillamine.

**Table S7.** Comparison of epidemiological characteristics of patients from Necker Hospital and other centers.

**Table S8.** Univariate analyses of associations between urine pH, urine specific gravity and cysteine-binding thiol (D-penicillamine and/or tiopronin) with the risk that a given patient will have cystine crystalluria.

**Table S9.** Univariate analyses of associations between urine pH, urine specific gravity, and cysteine-binding thiol agents (D-penicillamine and/or tiopronin) and the risk of a given patient having cystine crystal volume  $\geq 3000 \mu\text{m}_3 / \text{mm}_3$ .

**Table S10.** Association between urinary cystine excretion and cystine crystalluria.

**Table S11.** Univariate analyses of associations between urine pH, urine specific gravity and the risk of a given patient having calcium phosphate crystalluria.