Cystinuria: clinical practice recommendation

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Cystinuria (OMIM 220100) is an autosomal recessive hereditary disorder in which high urinary cystine excretion leads to the formation of cystine stones because of the low solubility of cystine at normal urinary pH. We developed clinical practice recommendation for diagnosis, surgical and medical treatment, and follow-up of patients with cystinuria. Elaboration of these clinical practice recommendations spanned from June 2018 to December 2019 with a consensus conference in January 2019. Selected topic areas were chosen by the co-chairs of the conference. Working groups focusing on specific topics were formed. Group members performed systematic literature review using MEDLINE, drafted the statements, and discussed them. They included geneticists, medical biochemists, pediatric and adult nephrologists, pediatric and adult urologists experts in cystinuria, and the Metabolic Nephropathy Joint Working Group of the European Reference Network for Rare Kidney Diseases (ERKNet) and eUROGEN members. Overall 20 statements were produced to provide guidance on diagnosis, genetic analysis, imaging techniques, surgical treatment (indication and modalities), conservative treatment (hydration, dietetic, alkalinization, and cystine-binding drugs), follow-up, self-monitoring, complications (renal failure and hypertension), and impact on quality of life. Because of the rarity of the disease and the poor level of evidence in the literature, these statements could not be graded. This clinical practice recommendation provides guidance on all aspects of the management of both adults and children with cystinuria, including diagnosis, surgery, and medical treatment.

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Cystinuria (OMIM 220100) is an autosomal recessive hereditary disorder characterized by a defective reabsorption of cystine and dibasic amino acids ornithine, lysine, and arginine in the renal proximal tubule and in the epithelial cells of the gastrointestinal tract. The cystine transporter is a heterodimer composed of 2 subunits joined by a disulfide bridge. The interaction of the heavy subunit rBAT and the light subunit $b^{0,+AT}$ is essential for the functional expression of the whole system $b^{0,+}$.[1] Two genes responsible for cystinuria have

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Table 1 | Summary of cystinuria disease classifications

Genotype classification	Type A, *SLC3A1* pathogenic variant(s)	Type B, *SLC7A9* pathogenic variant(s)	Mixed genotype
Protein	Heavy subunit rBAT	Light subunit $b^{0,+AT}$	rBAT and $b^{0,+AT}$
Examples of genotype	AA	BB	AAB, ABB, BBB
Inheritance	Autosomal recessive (genotype AA)	Autosomal recessive (genotype BB)	Mixed
Phenotype	Individuals with genotype AA have elevated COLA excretion and form kidney stones Carriers of genotype A0 usually have normal cystine excretion and do not develop cystine stones	Individuals with genotype BB have elevated COLA excretion and form kidney stones Carriers of genotype B0 often have elevated cystine excretion but rarely develop stones[7]	Individuals with genotype AAB, ABB, and BBB form kidney stones Carriers of genotype AB often have elevated cystine excretion but rarely develop stones[8]

COLA, cystine, ornithine, lysine, and arginine (4 amino acids whose excretion is increased in cystinuria).
Genotypes AA and BB denote 2 mutated alleles in *SLC3A1* or *SLC7A9*, respectively, whereas A0 and B0 denote the identification of only 1 mutated allele. There may be mixed genotype groups such as AB, where individuals have 1 pathogenic variant in *SLC3A1* and 1 in *SLC7A9*, and AAB and BBA if there are >2 pathogenic variants pertaining to different genes.

been identified: *SLC3A1* (2p21), which encodes the heavy subunit (rBAT), and *SLC7A9* (19q12), which encodes the light subunit ($b^{0,+AT}$).[2–4] High cystine excretion leads to crystal precipitation in the distal tubule and formation of cystine stones because of the low solubility of cystine at normal urinary pH.

Worldwide, the overall prevalence of cystinuria is 1 per 7000 with high ethnogeographic variation.[1] Two large studies performed in France show that cystinuria causes 1% of all cases of urolithiasis and 4% and 5% of urolithiasis in children.[5,6]

RECOMMENDATION

Classification and pathophysiology of cystinuria

Classification. Three phenotypes of cystinuria have traditionally been described on the basis of the urinary excretion of cystine in the obligate heterozygous parents (Table 1).[4,7–9] More recently, a genotypic classification of cystinuria was introduced[10] (Table 1). Most patients have genotype AA or BB, which denotes 2 mutated alleles in *SLC3A1* or *SLC7A9*, respectively. A0 and B0 denote the identification of only 1 mutated allele, even by extensive genotyping (see below). Carriers of genotype A0 usually have normal cystine excretion, whereas carriers of genotype B0 have often elevated cystine excretion but rarely develop stones.[8]

Genetic testing of cystinuria. *Method of screening.* Small variations can be detected by direct Sanger sequencing. For the detection of large rearrangements (e.g., copy number variations), multiplex ligation-dependent probe amplification or real-time polymerase chain reaction is required.[8,11] Next generation sequencing–based panel analysis should be favored over Sanger sequencing, as next generation sequencing–based panel approaches allow for both copy number variation analysis and the detection of single-nucleotide changes.

Identified mutations in *SLC3A1* and *SLC7A9* are presented in Supplementary Table S1. Large-scale rearrangements represent between 17% and 21% of all found variants.[8,11,12] In *SLC3A1*, known deletions and insertions often involve parts of the neighboring genes *PREPL* and *CAMKMT*.[8] Hypotonia-cystinuria syndrome (MIM 606407) is a rare homozygous contiguous gene deletion syndrome, removing part or all of *SLC3A1* and *PREPL* genes, associated with cystinuria type A. It is characterized by hypotonia, minor facial dysmorphism, mild to moderate intellectual disability, and growth hormone deficiency.[13–15]

Genotype-phenotype correlation. Although data are conflicting, neither the genotypic nor the previous phenotypic classification appears to be relevant with respect to the clinical course in patients with cystinuria. No difference in age of onset, number of stone emissions, or total stone events between those with type AA and those with type BB was detected.[10,12,16,17]

Role of genetic analysis in routine clinical practice. Genetic analysis is not mandatory for diagnosis, but is useful in the context of genetic counseling and in situations of clinical uncertainty. In cases with prenatal diagnosis of hyperechogenic colon, genetic testing can be recommended for the early diagnosis of cystinuria, as urinary amino acid excretion is difficult to interpret in the first months/years of life because of tubular immaturity.

Statements 1

- *Cystinuria* is characterized by a high urinary excretion of cystine and dibasic amino acids (ornithine, lysine, and arginine) due to a defective proximal tubular reabsorption.
- We suggest performing genetic analysis in patients with cystinuria, allowing one to confirm the diagnosis, to classify the disease, and to counsel other family members, although no strong genotype-phenotype correlations have been demonstrated.

Pathophysiology of cystine stones. The mechanisms involved in cystine kidney stone formation are related to the high concentration of cystine and its low solubility at normal urinary pH (Figure 1[21]). Cystine solubility is <250 mg/l (1.05 mmol/l) at pH <6 and reaches 500 mg/l (2.1 mmol/l) at pH >7.5.[18–20] The amount of cystine excreted by biallelic affected individuals (AA and BB) is typically >400 mg/d (1.6 mmol/d) and usually reaches 600 to 1400 mg/d (2.5–6 mmol/d), whereas it does not exceed 50 mg/d (0.2 mmol/d) in normal subjects.[21] Cystine reabsorption in the proximal tubule is not directly sodium dependent, but high sodium intake would increase the intracellular neutral amino acids and sodium load, which might slow the apical reabsorption of cystine[1,22–24]

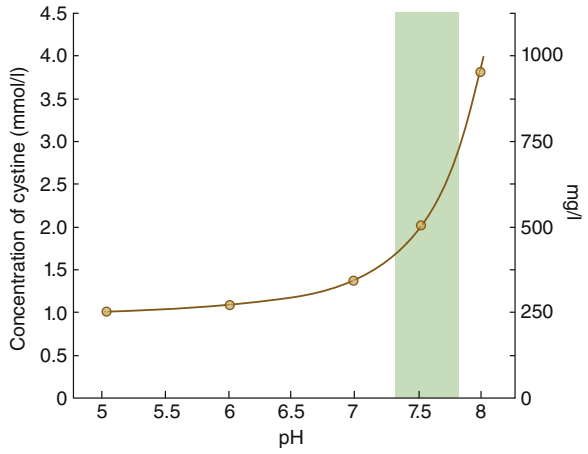

Figure 1 | Cystine solubility according to urinary pH. Adapted with permission from Bouzidi H, Daudon M. [Cystinuria: from diagnosis to follow-up]. *Ann Biol Clin (Paris).* 2007;65:473–481 [in French].[21]

Clinical presentation and diagnosis

Clinical presentation. Detection of hyperechoic colon during routine ultrasound before 36 weeks of gestation may suggest a diagnosis of cystinuria with a high positive predictive value (89%).[25,26] The proposed explanation of this observation is that cystinuric fetuses have high cystine concentration in the amniotic fluid. As the fetus constantly swallows amniotic fluid and the rBAT/b^{0+} transport system is exclusively expressed in the small intestine, ingesting amniotic fluid with high cystine content would result in an overload of the intestinal reabsorptive capacity, causing high cystine concentration and precipitation in the colon.[27] In any case, confirmation of the diagnosis should be made after the delivery. The first renal stone detection can occur early[10,28] and exceptionally at birth, suggesting the possible prenatal formation of the stones.[28,29]

In most of the patients, the first stone detection occurs during childhood or adolescence. The median age of the first clinical event was 13 years in a European cohort[10] and 16 years in a French study,[17] although the diagnosis can also be made during adulthood.[10,12,17,29–31] Type A cystinuria and type B cystinuria have a similar age at diagnosis and similar clinical evolution.[10,30] A more severe disease with a higher frequency of stone episodes has been reported in males in 1 study,[10] but not confirmed in other series.[12,17]

Cystinuria can be detected after the evaluation of a renal stone emission, hematuria, or urinary tract infections or occasionally during radiological examinations (radiograph and renal ultrasound scan) performed for other reasons.[17] The siblings of patients with cystinuria should be offered investigation for cystinuria as they could be asymptomatic.[32]

Statements 2

- Detection of hyperechoic colon during routine ultrasound before 36 weeks of gestation may suggest a diagnosis of cystinuria with a high positive predictive value.
- In patients with cystinuria having syndromic features, deletions on chromosome 2p21 including *SLC3A1* gene should be investigated.
- The first stone episode often occurs during adolescence.

Diagnosis of cystinuria. The diagnosis of cystinuria can be made by analysis of kidney stones, observation of cystine crystals in the urinary sediment, or detection of an abnormal excretion of cystine and dibasic amino acids in urine in adults and children.

The analysis of stone composition by infrared spectroscopy and X-ray diffraction offers the highest degree of certainty, whereas the wet chemical analysis of urinary stones is considered to be obsolete because of poor results.[33,34] Most cystine stones may be easily recognized by their morphological aspect (Figure 2a and b).

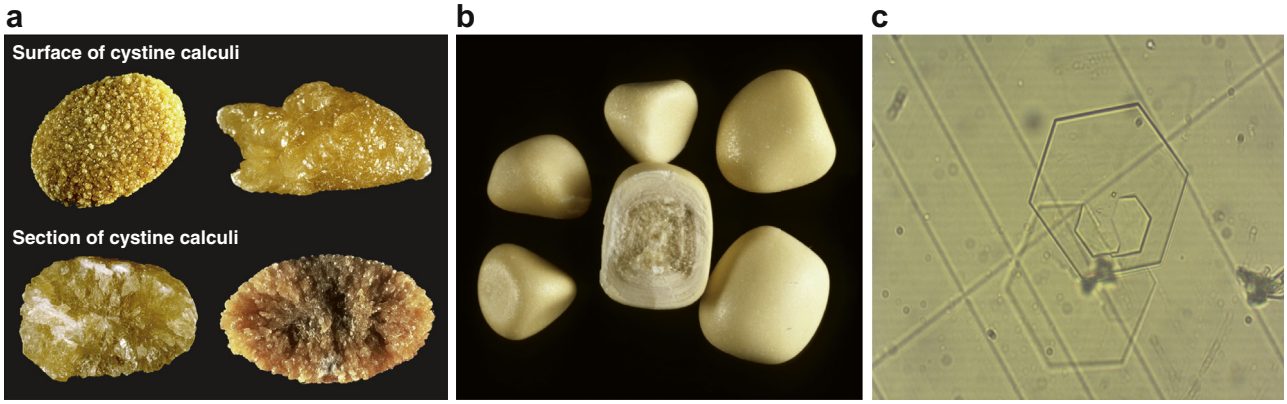

Figure 2 | Cystine stones. (**a**) Under microscopic examination, cystine stones appear yellow-brown and have a granular surface and crude and radial structure. (**b**) A different morphology is observed during alkaline therapy: these stones have a smooth or finely rough appearance because of incorporation in their peripheral layers some proportions of calcium phosphate, and the cystine crystals are often of reduced size. (**c**) Microscopic examination of the first morning urine specimen can reveal the characteristic crystals of cystine: large hexagonal crystals, lamellar appearance, and often stacked parallel to each other. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

Table 2 | Urinary cystine values

Variable	Urinary cystine excretion per day	Urinary cystine concentration
Reference values	<30 mg/d (0.13 mmol/d)	<1 mo: <39 μmol/mmol creatinine (<80 mg/g creatinine) <1 yr: <25 μmol/mmol creatinine (< 52 mg/g creatinine) >1 yr: <17 μmol/mmol creatinine (<35 mg/g creatinine)[36]
Cystinuria AA and BB genotypes	>400 mg/d (1.7 mmol/d)	>150 μmol/mmol creatinine (>315 mg/g creatinine)
Cystinuria A0 genotype	<100 mg/d (0.4 mmol/d)	
Cystinuria B0 genotype	40–400 mg/d (0.17–1.7 mmol/d)	

Cystine values depend on the method of analysis and on the studied population. Adapted with permission from Dello Strologo L, Pras E, Pontesilli C, et al. Comparison between *SLC3A1* and *SLC7A9* cystinuria patients and carriers: a need for a new classification. *J Am Soc Nephrol.* 2002;13:2547–2553[10] and Parvy PR, Bardet JI, Rabier DM, Kamoun PP. Age-related reference values for free amino acids in first morning urine specimens. *Clin Chem.* 1988;34:2092–2095.[36]

Microscopic examination of the first morning urine sample, or even a random urine sample, can reveal the characteristic hexagonal crystals of cystine, which are highly specific for the diagnosis (Figure 2c). At least two-thirds of untreated patients will manifest these pathognomonic crystals.

The diagnosis of cystinuria can be confirmed by the measurement of elevated levels of cystine and dibasic amino acids (ornithine, lysine, and arginine) in 24-hour urine specimens. For small children who cannot yet control their voiding, the first or second morning urine specimens are the most suitable and results should be reported relative to the creatinine level to compensate for urine concentration (Table 2[10,36]).[35–37] Although ion exchange chromatography is generally considered to be the reference method, liquid chromatography–tandem mass spectrometry is increasingly used as a routine methodology, and both methodologies could be considered as appropriate.

Genetic testing is not mandatory for diagnosis. It may be performed in specialized centers in case of atypical presentation, uncertain mode of inheritance, and for genetic counseling and/or research purpose (see "Classification and pathophysiology of cystinuria" above). Increasingly, genetic screening of patients with stone disease (children or adults) using stone-oriented next generation sequencing panels may reveal pathogenic genetic variations in *SLC3A1* and *SLC7A9*. Because not all variants are pathogenic, the interpretation of causality needs careful assessment and genetic result should be consistent with the clinical and biochemical findings.

The cyanide-nitroprusside test is a rapid qualitative test that has been classically proposed as a screening method for cystinuria.[38] However, because of its low reproducibility and sensitivity and the use of hazardous and unstable reagents, this test is considered outdated.

Statements 3

- Infrared spectroscopy and X-ray diffraction offer the highest degree of certainty for the analysis of cystine stone composition.
- Microscopic examination of the first morning urine specimen can reveal the characteristic hexagonal crystals of cystine, which are highly specific for the diagnosis of cystinuria.
- The diagnosis of cystinuria is confirmed by the measurement of increased levels of cystine and dibasic amino acids (ornithine, lysine, and arginine) in 24-hour urine specimens or in spot urine sample (as amino acid/creatinine ratio).

Imaging techniques used for diagnosis in children and adults. The diagnosis of cystinuria is not based on imaging. For the diagnosis of stones in general, noncontrast computed tomography scan of kidneys, ureters, and bladder (CT KUB) offers highest sensitivity and specificity[39] and is often obtained before surgical intervention. Radiation dose can be minimized with low- and ultra–low-dose techniques, but this is dependent on body mass index.[40] The use of Hounsfield units in cystine stones is of limited benefit because of the narrow range, most typically <800 units, despite generally being considered hard stones.[41]

However, assessment and surveillance with ultrasound may be more appropriate in recurrent stone formers in preference to a radiograph of kidneys, ureters, and bladder or CT KUB to reduce the cumulative radiation exposure.[42] In children, ultrasound is often used a first-line investigation, with low-dose CT KUB as a second-line investigation.

Contrast CT intravenous pyelogram is only occasionally needed to delineate anatomy and plan surgery in selected patients.[43]

Statements 4

- Noncontrast CT KUB offers the highest sensitivity and specificity for detecting renal and ureteral stones. Low-dose and ultra–low-dose techniques should be used as they have been shown to maintain sensitivity and specificity in stone detection.
- Assessment and surveillance with ultrasound may be more appropriate in recurrent cystine stone formers to minimize the cumulative radiation exposure from CT KUB.
- In children, ultrasound should be used as the first-line diagnosis imaging technique.

Treatment

Treatment of acute renal colic. The classical symptomatic treatment of renal colic should be used with urologists involved in the management of patients from admission. Consideration should be given to analgesia requirements and signs of infection to assess whether there is a need for urgent decompression (stent or nephrostomy).[44,45] In patients with refractory pain or those with a low probability of passing the stone with conservative management, ureteroscopic stone removal or extracorporeal shockwave lithotripsy (ESWL) should be undertaken in a timely manner. Stone size and location are used to guide discussions on the chance of spontaneous stone passage. In a recent large real-world study of all stone formers managed conservatively, the chance of spontaneous stone passage was 89%, 49%, and 29% for stones <5, ≥5–7, and >7 mm, respectively.[46] For stones in the proximal and distal ureter, the passage rates were 52% and

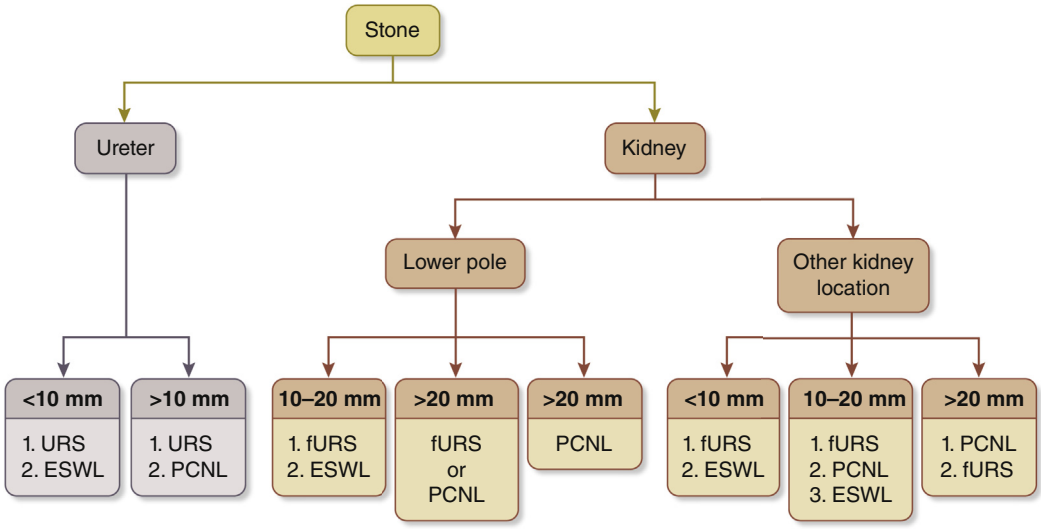

Figure 3 | Surgical treatment algorithms. ESWL, extracorporeal shockwave lithotripsy; fURS, flexible ureteroscopy; PCNL, percutaneous nephrolithotomy; URS, ureteroscopy.

83%. However, patients with cystinuria may be able to pass larger stones because of multiple previous stone passage and knowledge of previous ability to pass stones is important.

Statements 5

- A nonsteroidal anti-inflammatory drug should be the first drug of choice in the absence of contraindications.
- Renal decompression (with stent or nephrostomy) should be undertaken in patients with infected or obstructed kidneys.

Medical expulsive therapy. There is no specific evidence for the use of medical expulsive therapy in patients with cystinuria, and its use will depend on local policies.

Surgical treatment. *Indications for surgical treatment.* *Ureteral stones.* When observation is the strategy offered to a patient with an uncomplicated ureteral stone (i.e., absence of infection, no refractory pain, and no deterioration of renal function) that may pass spontaneously, surgical treatment should be considered if the stone fails to pass after a reasonable period of conservative treatment not exceeding 4 weeks from initial clinical presentation to prevent further symptoms or renal insult.[47,48] Also, in case of complication during this period of time, such as persistent pain despite adequate analgesic medication, or persistent obstruction, surgical treatment should be offered.[49] In cystinuria, because of the recurrent nature of stones and higher incidence of chronic kidney disease (CKD), once a decision to treat is made, this should be expedited in a timely fashion.[50]

Statement 6

- Patients with cystinuria and ureteral stones who are well with no infection or renal impairment can be observed for a period of up to 4 weeks for stone passage. Ongoing pain, renal impairment, and low chance of spontaneous passage are indications for prompt treatment.

Renal stones. Surgical management of cystine renal stones does not differ significantly from other stone compositions.[51–53] However, because of frequent recurrent episodes, complete stone clearance is of importance, where possible, to avoid growth of residual fragments, which may result in symptoms or further surgery later.[54] Small renal stones may be observed with periodic evaluation as they may pass. Larger renal stones >1 cm, pain, infection, hematuria, and stone growth are indications that should prompt surgical intervention.[55] In pediatrics, because of the fast stone growth rates and new stone formation, patients should be rendered stone-free whenever possible. However, repeated operations can also potentially damage the kidney and should be evaded by optimizing conservative treatment.

Statement 7

- Because of the recurrent nature of cystine stones, complete stone clearance should be achieved whenever possible.

Surgical modalities (Figure 3a and b). ESWL, ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL) are all options for treating cystine stones (Figure 3).

Although cystine stones are generally considered harder and more resistant to ESWL, reasonable outcomes can be achieved by well-trained urologists in adults and children.[56–60] URS is the mainstay of treatment of ureteral stones and renal stones <20 mm in children and adults.[48,52,61] Although PCNL is recommended for renal stones >20 mm, staged ureteroscopic procedures may be offered because patients with cystinuria often have had multiple previous invasive procedures and high recurrence rates, thus demanding the use of the least invasive methods.[52,62] When PCNL is undertaken, newer miniaturized techniques may be beneficial in reducing trauma to the renal parenchyma in recurrent stone formers.[61,63]

Table 3 | Methionine content of several foods

Food item	Content (mg/100 g)
Dried cod	2300
Horse meat	1300
Crayfish	1000
Sardines in oil	740
Tuna in oil	680
Other fish	600
Liver	600
Poultry meat	550–620
Other meat (pork, beef, mutton, and veal)	400–550
Parmesan cheese	930
Gruyère cheese	900
Emmental cheese	790
Other cheese	500–600
Eggs	390

Modified with permission from Bouzidi H, Daudon M. [Cystinuria: from diagnosis to follow-up]. *Ann Biol Clin (Paris).* 2007;65:473–481 [in French].[21]

If ureteral stent placement is considered at the end of an endourological procedure (URS or PCNL), the time of indwelling should be minimized because of the risk of encrustation, which can occur within 2 weeks.[52]

Statements 8

- Patients with cystinuria often undergo frequent procedures; therefore, ureteral stones and renal stones <20 mm should be treated with flexible URS to avoid the insult of PCNL.
- Although often considered relatively ESWL resistant, patients with previous treatment success or patients who wish to avoid invasive procedures, including children, may be offered ESWL.
- When PCNL is considered, miniaturized techniques may offer stone-free rates equivalent to that with standard PCNL but with reduced renal insult.
- Stent dwell time should be ideally minimized to <2 weeks because of the risk of rapid encrustation.

Differences in surgical treatment between children and adults. Usually the treatment strategies in children are the same as in adults. ESWL is likely to be performed under general anesthesia in children. Small recent series suggest ESWL is less frequently used today because of advances in pediatric URS.[61,64] URS in young children requires specific equipment (miniaturized ureteroscopes) and specialized surgical expertise. Besides stone-related factors, sex (in children) and age of the patient have to be considered when making a choice between retrograde and percutaneous treatment. For percutaneous surgery, miniaturized techniques (mini and ultramini PCNL) should be used.[63] In young children, urological procedures are associated with higher morbidity. Open surgery in pediatric cases should be limited but may be required in cases of congenital anomalies of the kidney and urinary tract. Staghorn calculi may be approached with a combination of PCNL and ESWL and occasionally with open surgery.

Conservative treatment. *Hydration.* Fluid intake should guarantee a urine output large enough to maintain a cystine concentration of <250 mg/l (1 mmol/l) during 24 hours.[21,65] In adults, >3 L of urine output is required for excretion of 1 to 1.5 g (2–3 mmol) of cystine per day.[19,66] The target of urine specific gravity should be ≤1.005.[67] In children, these values may be adjusted to promote a 24-hour urine volume of >2 l/1.73 m^2.[68] Patients should be strongly advised to consume fluids before bedtime and upon awakening. In some refractory pediatric cases, it could be considered to provide water during the night by mean of nasogastric tube feeding or gastrostomy.

Statements 9

- Fluid intake should guarantee a urine output large enough to maintain a cystine concentration of <250 mg/l (1 mmol/l).
- In most adults, at least 3 l of urine output per 24 hours are required.
- In children, urine volume should be higher than 2 l/1.73 m^2.

Dietetic. The effect of a low-sodium diet on reducing cystine excretion, albeit modest, has been demonstrated.[69–72] Reducing sodium intake to 1 to 1.5 mEq/kg (in adults 100 mEq/d or NaCl 6 g/d) is therefore advisable even if its effect on stone activity is not supported by clinical trials.[21]

Reduced methionine intake lowers cystine production, but it should not be below the physiological requirement (i.e., 1200–1400 mg/d in adults).[73] Such reduction can be partially achieved by avoidance of foods with high methionine and cystine content (Table 3[21]). For adults, protein intake should be lower than 1 g/kg (ideal weight) per day to reach this goal. Restriction of animal protein intake also decreases net acid excretion, increasing urine pH. However, its potential effect has not been demonstrated in clinical trials. Protein restriction is not advisable in children for concern about growth, but foods with high methionine content should be reduced.[73]

Statements 10

- Reducing sodium intake to 1 to 1.5 mEq/kg (adults 100 mEq/d or NaCl 6 g/d) is recommended.
- Reduced methionine intake is recommended to lower cystine production.

Alkalinization. To increase cystine solubility, alkalinization should be a cornerstone of treatment for all patients. Potassium citrate, 60 to 80 mEq/d (60–80 mEq/1.73 m^2 in children), should be preferred as alkalinizing agent, because it provides effective alkalinization without increasing sodium output.[72,74] In adults, the starting dose around 60 mEq/d should be carefully adjusted until therapeutic urinary pH values are reached in each urine portion in freshly voided urine (7.5–8.0).[67,75,76] There is a risk of calcium-phosphate crystal formation at high pH value.[67] Potassium citrate should be given in 3 to 4 single doses (including large bedtime dose) or diluted in large volumes of water. Sodium bicarbonate is mainly recommended in cases with severe renal insufficiency or intolerance to potassium citrate, although sodium increases urinary cystine excretion.[75] Although acetazolamide has been suggested as an additional mean to increase urine pH, it is not well tolerated and has not been shown to be superior to citrate.[1,77]

We recommend to reinforce medical therapies at the time of any urological intervention for stone removal.[78]

Statement 11

- Potassium citrate, 60 to 80 mEq/d, is preferred as alkalinizing agent and adjusted until therapeutic pH values (7.5–8.0) are reached in each urine portion during 24 hours. Urinary pH should be measured in freshly voided urine.

Cystine-binding drugs. Tiopronin and D-penicillamine are sulfhydryls that cleave cystine into 2 cysteine moieties to form a mixed disulfide.[79] The solubility of the cysteine-penicillamine complex is up to 50-fold higher than that of cystine.[1] These thiol-containing agents can be used in patients who have stone recurrence despite good adherence to the above interventions. Tiopronin and D-penicillamine are both effective treatment in reducing free urine cystine levels.[10,20,80,81]

However, cystine-binding agents carry severe adverse effects. It has been suggested that serious adverse events are less common with tiopronin, but a large recently published study showed that the incidence of adverse effects was similar for the 2 drugs.[17,67,82] Adverse effects include alterations in taste perception, mucocutaneous lesions, proteinuria and/or nephrotic syndrome due to immune complex membranous glomerulopathy,[17,83–85] and immune-mediated diseases.[68] Severe hematological reactions such as neutropenia and thrombocytopenia can also occur.[86]

Monitoring complete blood cell count and urinary protein excretion should be performed regularly. Because of potential long-term effects of these agents, the duration of treatment should be evaluated case by case.

The optimal dosage varies from patient to patient.[80] For tiopronin, the dosage is between 15 and 40 mg/kg/d in 3 divided doses (in adults 800–1500 mg/d divided in 3 doses) and around 20 to 30 mg/kg/d in 4 divided doses (maximum dosage 1.2 g/d) for D-penicillamine.[21,75,80] We suggest a higher dose to be given at bedtime.

Statements 12

- Conservative treatment is based on a stepwise strategy, using hydration, diet, and alkalinization as basic measures, with the addition of thiol derivatives in refractory cases.
- Monitoring of complete blood cell count and urinary protein excretion should be performed regularly in patients treated with thiol derivatives.

New therapeutic options. New drugs L-cystine diamides have recently been proposed as L-cystine crystallization inhibitors for cystinuria,[87–90] but their routine clinical use has not yet been validated. α-Lipoic acid inhibits cystine stone formation in mice, and its use has to be further evaluated in humans.[91,92]

Patients' follow-up

Imaging techniques. Published clinical series have used a combination of periodic ultrasound and noncontrast CT KUB[66,78] or ultrasound only,[52,80] with noncontrast CT reserved as a second-line investigation. The frequency of follow-up is variable and determined upon clinical review.[52]

Statements 13

- Offer ultrasound as first-line imaging in the follow-up of patients with cystinuria, with noncontrast CT as a second-line investigation.
- The frequency of follow-up varies from every 3 months to annually, depending on the activity of stone formation.

Role of crystalluria. A positive association has been shown between stone activity and crystalluria in urine samples.[93–95]. The optimal timing of the urine sample for assessing crystalluria is debated, with some authors showing positive association of stone activity with samples obtained during clinical visits[93] and others with early morning urine samples.[67,94] In principle, monitoring crystalluria may allow tailoring of radiological investigations, but prospective studies are needed.

Statement 14

- Crystalluria is a useful tool in the management of patients, but assessing crystalluria requires standardized methodology that is not available in some centers.

Urinary cystine monitoring. Cystine coexists in urine specimens in soluble and nonsoluble forms.[52] Their relative proportion is dependent on several factors, including urinary pH, ionic strength, and urine concentration.[96] Total urinary cystine is not a good predictor of the clinical outcome.[97] Measurement of cystine concentration in fractionated urinary collections may help monitoring the adequacy of the therapy.[65]

Measuring free and bound cystine has a clinical value in patients treated with cystine-binding drugs to adjust treatment dose (target level of free cystine <100 μmol/mmol creatinine), but it is not available in all centers and the results of published studies need to be replicated.[80,98]

Statement 15

- Monitoring urinary cystine is of limited value in the management of patients with cystinuria.

Monitoring of other urinary parameters. Monitoring frequency depends on disease activity. In patients with rare stone events (<1 per year), yearly monitoring is sufficient. In adults and children who are able to collect 24-hour urine specimens, we suggest monitoring 24-hour urine specimens to assess urinary volume, sodium, and creatinine excretion. Monitoring proteinuria should be recommended in 3 situations: (i) when cystine-binding thiols are used, (ii) in case of surgery-induced nephron reduction, and (iii) in case of renal failure. Measuring calcium excretion is useful in patients with mixed stone composition.[99,100] If patients cannot collect 24-hour urine specimens, monitoring urine density in spot samples at different times of the day helps assessing urinary dilution.

Statement 16

- In adults and children who are able to collect 24-hour urine specimens, we suggest monitoring 24-hour urine specimens to assess urinary volume, sodium, and creatinine excretion and proteinuria.

Supersaturation tests. Measuring supersaturation may reduce the variability in cystine excretion that is related to differences in urinary cystine solubility.[101,102] A proprietary assay has been developed to determine cystine capacity by measuring the solubility of cystine added to urine samples. The results of this assay correlate with stone activity, although the test lacks sensitivity,[103] limiting its clinical usefulness. Assessing urine supersaturation may also be helpful to evaluate the efficacy of cystine-binding thiol drugs, which reduce supersaturation.[20]

Statement 17

- Urinary supersaturation tests may be useful to evaluate the efficacy of therapy, but they are available only in a few specialized centers through a single commercial US laboratory.

Stone activity. Different criteria of stone activity such as changes in stone size, development of new stones, passages of stones or interventions for stones, or a combination of the above have been proposed.[10,104,105] Establishing a validated methodology would be valuable for clinical research.

Role of self-monitoring. Although prospective studies demonstrating the benefits of self-monitoring are not available, compliance with treatment, including alkalizing agents, has been associated with fewer urological interventions.[105] Density should also be measured in spot morning urine samples (objective <1005).[67] Lower densities are associated with a reduced risk of cystine crystalluria.[67,106] Recently, smartphone applications have been developed to remind patients to drink and to monitor water intake.

Statements 18

- All patients should self-monitor urinary pH to maintain values between 7.5 and 8.

  This can be achieved with test strips, dipsticks, or electronic devices.
- Assessing urinary specific gravity may also be useful.

Pregnancy. The absence of stones should be assessed before pregnancy. When possible, patients should be stone-free before pregnancy. There is an increased risk of stone formation in general during pregnancy because of anatomical factors and hypercalciuria. Cystine-binding thiols are contraindicated. As it is an autosomal recessive disease, the risk of transmission to children is extremely low unless the other parent is a carrier of a pathogenic variant in the same gene.

Complications

CKD and high blood pressure. On average, patients with kidney stones are at higher risk of CKD than the normal population.[107] This risk is considerably higher in cystine stone formers.[108] The majority of adults with cystinuria have estimated glomerular filtration rate (eGFR) $<$ 90 ml/min per 1.73 m^2.[12,17,31,50,52] Most often, they have eGFR ranging from 60 to 89 ml/min per 1.73 m^2. The incidence of end-stage kidney disease remains relatively low.[12,17] However, in 1 study including 314 adult patients (mean age, 38.7 years), 26.8% of patients had eGFR $<$ 60 ml/min per 1.73 m^2 and 12% had proteinuria.[17] In another recent study, 17.8% of patients had eGFR $<$ 60 ml/min per 1.73 m^2.[50]

The risk of CKD is closely related to age and to history of renal parenchymal damage, including previous nephrectomies, congenital abnormalities, and renal hypoplasia.[17,50,109] A proteomic study suggests a potential role for inflammation in kidney damage in cystinuria.[110] There is no risk of relapse after renal transplantation.[111]

Hypertension is reported in 29% to 51% of adult patients with cystinuria and is associated with male sex, age, and CKD.[17,50] Another study found no difference in blood pressure between cystine and noncystine stone formers but patients with cystinuria were 10 years younger.[108]

Statement 19

- Patients with cystinuria are at higher risk of CKD and early-onset hypertension.

Adjustment of treatment as stone activity decreases with renal failure. Data on dose adaptation of chelating agents in patients with CKD are insufficient. Theoretically, patients with CKD decrease their urinary cystine excretion and consequentially their risk of forming new stones if their urine output remains elevated. Because chelating agents are predominantly eliminated by the kidneys, they tend to accumulate during renal impairment. The risk/benefits of using these drugs should be carefully evaluated in patients with CKD. Treatment should be discontinued or reduced in patients with eGFR 60 to 89 ml/min per 1.73 m^2 and should always be discontinued in patients with lower eGFR.

Impact on health-related quality of life. Adult patients with cystinuria have on average a poor health-related quality of life than does the general population.[106,112] Health-related quality of life scores are positively influenced by the duration of stone-free time since the last event.[112] Many patients express frustration and find that medical treatment is poorly effective or poorly tolerated.[106] Comparisons of health-related quality of life between cystinuric and noncystinuric stone formers have yielded conflicting results.[112,113] Different questionnaires have been used, including the Short-Form (36) Health Survey in the US population.[106,112] Stone-specific questionnaires, including Wisconsin Stone Quality of Life questionnaire, have also been developed,[113] but are not yet validated in different populations.

Statement 20

- Patients with cystinuria and active stone disease have a poor health-related quality of life than does the general population.

Conclusion

Overall 20 statements were produced to provide guidance on diagnosis, genetic analysis, imaging techniques, surgical treatment, conservative treatment, follow-up, self-monitoring, and complications (renal failure and hypertension), both in adults and in children.

Briefly, the diagnosis can be made by analysis of kidney stones, observation of cystine crystals in the urinary sediment, or detection of an abnormal urinary excretion of cystine. Because of the recurrent nature of cystine stones, complete stone clearance should be achieved whenever possible with a patient-specific surgical approach. Conservative treatment is based on a stepwise strategy, using hydration to maintain cystine concentration $<$ 250 mg/l, reduced sodium and methionine diet, and alkalinization with potassium citrate (to reach urinary pH 7.5–8) as basic measures, with the addition of thiol derivatives in refractory cases.

Several aspects apparently differ between these European recommendations and a recently published US consensus paper.[114] Strengths of the present article are the description of detailed genetic testing, comprehensive urinary cystine values facilitating the clinical diagnosis, and description of the specificities of surgical management. The recommended urine pH target is 7.5 to 8.0 in accordance with previous European guidelines and a recent publication.[67,76] In Europe, the detection and quantification of cystine crystals are used by many centers to monitor the conservative treatment of cystinuria.

We believe that this recommendation will have a positive impact on the outcomes of patients by establishing common standards as well as spreading and harmonizing good practices.

METHODS

Development of these clinical practice recommendations is an initiative of the European Reference Network for Rare Kidney Diseases (ERKNet) in collaboration with the European Reference Network (ERN) for rare and complex urogenital diseases and conditions (eUROGEN), spanned from June 2018 to December 2019, and involved 1 meeting in Paris in January 2019 to discuss selected topic areas chosen by the co-chairs of the conference. This joint recommendations development group included geneticists, medical biochemists, pediatric and adult nephrologists, and pediatric and adult urologists. Working groups focusing on specific topics were formed. Group members performed systematic literature review using MEDLINE/PubMed and the Cochrane Library. The following key words were used: *cystine*, *cystinuria*, *penicillamine*, and *tiopronin*. A total of 1754 articles were initially identified, and articles relevant to the topic of diagnosis and management of cystinuria were selected (487 articles). Case reports were excluded. A total of 148 articles were assessed, and 115 were finally selected. Statements were elaborated and discussed by experts according to their level of agreement after literature review. Because of the rarity of the disease and the poor levels of evidence in the literature, these statements could not be graded. Revisions were made by external specialists including a patient group representative.

DISCLOSURE

BK reports advisory board activity with Advicenne. AB-T is an investigator of the Advicenne study ADV7103. MB, KT, MD, and EL report consulting fees by Advicenne. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. *SLC3A1*, reported genetic variants (HGMD 2018.4) missense/nonsense.

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