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Author contributions

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Competing interests

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Additional information

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cannot be met in low-resource countries. Nevertheless, they represent standards that should be striven for to improve the prognosis of cystinosis worldwide.

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Box 10 | Ophthalmological involvement

- We recommend that patients with cystinosis should be treated with a combination of cysteamine eye drops and systemic cysteamine; the latter is necessary to reduce the risk of permanent vision loss secondary to posterior segment complications (evidence-based, strong consensus)
- We do not recommend favouring one formulation of cysteamine eye drops over another. The formulation should be selected based on availability and tolerability (evidence-based, strong consensus)
- We suggest that patients with cystinosis should be prescribed cysteamine eye drops with or without benzalkonium chloride at any age (evidence-based, strong consensus)
- We suggest slit-lamp examination as a minimum assessment of corneal crystals in all patients with cystinosis (evidence-based, consensus)
- If available, we suggest using corneal imaging in addition to slit-lamp examination to improve the assessment of corneal crystal depositions over time and to motivate patients by providing them with an objective evaluation of corneal crystal depositions (evidence-based, consensus)
- We do not recommend the preferential use of any particular corneal imaging technique (that is, slit-lamp photography, anterior segment optical coherence tomography (AS-OCT), corneal densitometry, or in vivo confocal microscopy (IVCM)) in addition to slit-lamp examination (evidence-based, consensus)

relationships and role changes) and psychosocial aspects (for example, self-perception). This process involves a significant shift from a family-centred lifestyle to an independent approach to life, which can cause considerable anxiety for patients and their families. Rare diseases, such as cystinosis, pose additional transitioning challenges owing to the limited expertise often encountered in adult units. To avoid patients disengaging from their follow-up visits, which carries a significant risk of adverse outcomes^{28,59,73}, optimal health care transition coordination is needed. If patients have already undergone kidney transplantation before transition, non-adherence increases the risk of graft rejection^{190–193}.

Transition strategies need to be adapted to the patient age and CKD status, especially in those with advanced CKD or who have received a transplant. Protocols should always include screening for psychological, psychosocial and financial problems. Reports on the efficacy of a structured transition process on the outcome of adult patients with cystinosis are scarce, but guidelines are available for people with kidney diseases or with rare diseases¹⁹⁴. In general, joint consultations with different specialists, support in scheduling appointments, workshops and projects aimed at increasing health literacy, as well as dedicated websites, apps and chat rooms have moderate positive effects^{195,196}. Randomized controlled studies have not yielded convincing data^{195,197} and no cystinosis-specific studies are available, but a few tentative transition models have been proposed for people with cystinosis^{198,199} (Box 11).

Integrated care

The World Health Organization has defined integrated care as the “organization and management of health services so that people get

the care they need, when they need it, in ways that are user friendly, achieve the desired results and provide value for money”²⁰⁰. Patients with infantile nephropathic cystinosis or juvenile cystinosis are usually cared for by paediatric nephrologists as children and later by adult nephrologists because the kidneys are always affected. This bias carries the risk that other symptoms might be underestimated if patients are not followed in units that have expertise in treating cystinosis. Although no specific data are available, integrated care models seem to have positive effects on HR-QOL of patients²⁰¹ and cost-containment²⁰². In addition, integrated care models promote exchanges among specialists and increase the expertise of the entire group^{203,204}.

The implementation of integrated care for patients with cystinosis depends on the health care structure, health care systems, availability of specialists and financial resources. Integrated care models should always align with patient needs and competencies, avoid overloading patients with excessive information, and be aimed at limiting the number of clinic visits. Importantly, the needs of patients evolve as they become older and develop more symptoms.

A case manager that coordinates the care of individual patients should always be designated to ensure a patient-centred approach. Whenever possible, registries should be used to collect data and assess the effectiveness of interventions at the local, national or international levels¹⁸⁸ (Box 11).

Conclusion

Cystinosis is a rare multisystemic disease associated with substantial morbidity and low quality of life. The introduction of cysteamine treatment in the 1980s, which remains the only available medication for cystinosis to date, and advances in the treatment of kidney failure, have enabled patients to live well into adulthood. However, most individuals with cystinosis experience an increasing number of systemic symptoms as they age. In addition, cysteamine has considerable side effects, which often limits treatment adherence. The management of patients with cystinosis requires integrated care adapted to the needs of each patient. The professionals that make up the multidisciplinary team must change as the patient moves through the different phases of life, with special attention needed in the challenging period of transition from paediatric to adult care. We recognize that many of the recommendations discussed here

Box 11 | Addressing psychosocial needs, planning transition and promoting integrated care

- We recommend that the psychosocial needs of people with cystinosis of all ages and their families (including siblings) be assessed and that appropriate psychosocial support be provided to enhance the efficacy of medical care, and to promote the participation and mental health of patients and their families (evidence-based, strong consensus)
- We recommend implementing transition programmes for adolescents with cystinosis (expert-based, strong consensus)
- We recommend that, whenever possible, all patients with cystinosis be followed in institutions that offer an integrated care model. If not available, we recommend favouring an integrated care model (expert-based, strong consensus)

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Table 4 | Ophthalmological evaluation in people with cystinosis

Prioritization	Ophthalmic and medical history	Ocular symptoms	Vision assessment	Anterior segment examination	Posterior segment examination
Essential	Ophthalmic and medical history required at each visit	Recorded at each visit, including side effects of ocular medications	Age-appropriate visual acuity assessment Refraction should be measured at baseline	Slit-lamp biomicroscopic examination of anterior segment including conjunctiva, cornea, iris, lens to assess crystal deposition including fluorescein staining and intraocular pressure assessment	Dilated funduscopy (including optic nerve) at least annually to rule out papilloedema; peripheral retinal examination to identify any pigmentary retinopathy
Desirable	Recording of compliance with prescribed ocular medication	Grading of photophobia and other ocular surface symptoms using standardized scoring systems	LogMAR visual acuity measurement or equivalent	Slit-lamp imaging to assess corneal cystine crystal score; other measurements might include anterior segment OCT, corneal densitometry or IVCM	Retinal imaging using wide-angle fundus camera OCT disc and macula
As required according to clinical findings or symptoms	Other visual difficulties or eyesight-related issues	Other symptoms elicited as directed by clinical history (for example, visuospatial problems)	Contrast sensitivity; colour vision Refraction should be updated periodically	Any other ocular abnormalities, including issues with alignment or motility, external eye findings, eyelid margin or meibomian gland	Visual fields and electrodiagnostics performed if evidence of retinal involvement or optic nerve disease Fluorescein angiography, OCT-angiography or indocyanine green angiography as indicated, for example, if evidence of subretinal or choroidal neovascular membrane

IVCM, in vivo confocal microscopy; LogMAR, logarithm of the minimum angle of resolution; OCT, optical coherence tomography. Ophthalmological evaluation should be carried out at least annually.

dictate the most appropriate modality for monitoring ocular complications. In infants, examination of the cornea should be conducted with the hand-held slit lamp, and the retina and optic nerve should be examined with the indirect ophthalmoscope. Cooperative older children and adults can undergo more detailed examinations and imaging modalities. Whenever possible, ophthalmologists should document ocular findings using digital imaging modalities. These include slit-lamp and fundus photography, anterior segment-OCT, corneal densitometry and in vivo confocal microscopy. These techniques enable the comparison of results over time and the provision of important feedback to patients. Retinal involvement might be detected by widefield digital retinal imaging, OCT, visual field assessment and electroretinography.

Topical cysteamine treatment should be started as soon as corneal crystals are visualized. Two commercial preparations are available; alternatively, custom-made eye drops can be prescribed. Clinicians should select a preparation based on availability and/or tolerability. Eye drop formulations differ in the number of required daily applications. Of note, custom-made eye drops tend to be less stable (Supplementary Box 4).

Whether preventive treatment (that is, before corneal cystine crystals have developed) is useful remains unclear. In very young children with few crystal depositions, clinicians might defer starting topical therapy until the family has become comfortable with systemic therapy. Long-term adherence to topical therapy represents a frequent problem and usually decreases during adolescence and early adulthood. Adapting schedules to patient daily activities might improve compliance. Patients with intense photophobia usually have better adherence to therapy. Some patients might become sensitized to compounds used to stabilize eye drops, in particular benzalkonium chloride. Custom-made formulations that do not contain

these compounds should be tried in these patients^{185,186}. Applying preservative-free lubricant eye drops before cysteamine drops might also alleviate discomfort (Box 10).

Psychosocial needs, transition and integrated care Health-related quality of life

Studies have documented low health-related quality of life (HR-QOL) in individuals with cystinosis^{187,188}. Patients and their families have multiple and often unmet psychosocial needs that should be addressed. The burden of managing a chronic illness like cystinosis, in addition to uncertainties about the future and the need for continuous medical interventions, create psychological challenges.

HR-QOL is significantly influenced by age, gender, disease severity, social context, and other socioeconomic and psychological aspects¹⁸⁹, which should always be considered. Instruments to assess and address cystinosis-specific needs and challenges are currently lacking. Although positive effects of psychosocial support during transition from paediatric to adult care have been demonstrated in other diseases, such as cystic fibrosis, similar evidence is not available for cystinosis. The lack of patient- and family-centred care in many institutions worsens the situation because physicians are often unaware of the unique challenges that affect individuals with cystinosis and their families. Finally, access to psychosocial support is influenced by socioeconomic factors, language barriers and the availability of support services (Box 11).

Transition from paediatric to adult care

During the transition period, patients gradually become more independent in all areas of life, including logistics (for example, leaving home), financial decisions, social aspects (for example,

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Current recommendations for pregnancy in people with CKD also apply to those with cystinosis^{166–171}.

The major determinants of maternal complications during pregnancy (including electrolyte imbalances, worsening of CKD and preeclampsia¹⁷¹) are the severity of CKD, hypertension and proteinuria^{172,173}. Foetuses are also at a higher risk of intrauterine growth retardation, prematurity and death¹⁷¹.

Preeclampsia might develop in up to 50% of people with cystinosis, most of whom will have undergone kidney transplantation prior to pregnancy^{166,168,169,174,175}. By contrast, the rate of preeclampsia in women with a kidney transplant for other diseases ranges from 8% to 45%^{173,176}. A large proportion of women with cystinosis undergo a caesarean section because of prematurity, preeclampsia or cephalo-pelvic disproportion^{168,169}.

Although breastfeeding has substantial benefits, delaying reintroduction of cysteamine until after the breastfeeding period might have avoidable long-term adverse consequences for the mother. These considerations should be discussed on a case-by-case basis. Current data on the safety of cysteamine in infants of breastfeeding mothers who have reintroduced systemic cysteamine treatment are insufficient. In one report of a single patient, cysteamine concentrations in breastmilk were minimal¹⁷⁷. The child was breastfed for 4 months and had typical growth and development at 18 months of age¹⁷⁷. Of note, systemic exposure to cysteamine secondary to eye drops is negligible. No warning on possible teratogenic effect related to cysteamine eye drops has been issued to date (Box 9).

Ophthalmological involvement

Ocular complications are a common cause of morbidity in people with cystinosis. Cysteamine therapy, both systemic and as eyedrops, can avert these complications when cystinosis is diagnosed early and treatments are followed diligently¹⁷⁸. Cystine crystals accumulate in virtually all ocular structures, including the cornea, conjunctiva, iris, lens, optic nerve, retina and choroid¹⁷⁹. Corneal crystals contribute

to photophobia and blepharospasm in people with cystinosis. Systemic cysteamine does not reach the avascular cornea; therefore, topical cysteamine is required to halt or reverse corneal crystal accumulation^{37,180}.

In sub-optimally treated eyes, significant corneal crystal accumulation can destabilize the corneal epithelium causing punctate keratopathy, erosions and filamentary keratitis. In advanced cases, sight-threatening complications such as peripheral corneal neovascularization, corneal scarring, band keratopathy and corneal decompensation might require specialized surgery¹⁸¹.

Systemic cysteamine treatment is necessary to minimize or prevent complications from cystine accumulation in internal ocular structures. Potential complications include posterior synechiae, which can cause pupillary block and secondary glaucoma¹⁸². Early signs of retinal involvement can be observed as pigmentary changes in the peripheral retina on examination. Crystals in the retina and choroid are observed as hyperreflective spots on optical coherence tomography (OCT). With advanced retinopathy, patients might develop symptoms of night blindness, reduced visual field, abnormal colour vision and central vision loss¹⁸³. Advanced retinopathy is uncommon in patients who receive early and adequate systemic cysteamine therapy. Increased intracranial pressure (that is, pseudotumour cerebri) can occur even in the setting of well-managed systemic disease (see the section on Cysteamine treatment). This effect can cause papilloedema (that is, optic nerve swelling), potentially resulting in vision loss¹⁸⁴. As papilloedema is treatable, all patients with cystinosis require regular comprehensive eye examinations to screen for this condition.

Age-appropriate ophthalmological testing and schedules should be used (Table 4). Yearly comprehensive eye evaluation, including slit-lamp examination and fundoscopy, are essential to optimize cysteamine topical therapy and prevent vision loss. Discomfort or photosensitivity can limit assessments and efforts should be made to minimize patient discomfort. Age and patient cooperation might

Box 9 | Management of hypogonadism, fertility issues, pregnancy and breastfeeding

Male fertility

- We recommend testing for hypergonadotropic hypogonadism, which can be demonstrated by low serum testosterone levels in the presence of elevated luteinizing hormone serum levels on repeated measurements obtained during morning hours (evidence-based, strong consensus)
- We recommend testosterone replacement therapy in post-pubertal patients with nephropathic cystinosis and hypergonadotropic hypogonadism (evidence-based, strong consensus)
- We recommend offering fertility screening to young males with nephropathic cystinosis as soon as the patient has reached puberty and is willing and able to provide a semen sample for analysis (expert-based, strong consensus)
- We recommend discussing semen cryopreservation with patients and their family before starting testosterone substitution (evidence-based, strong consensus)
- We recommend discussing the possibility of performing microscopic testicular sperm extraction (mTESE) in combination with cryostorage of testicular spermatozoa if no or insufficient

sperm is observed in the ejaculate, before starting testosterone substitution (expert-based, strong consensus)

Female fertility and pregnancy

- We recommend a detailed risk assessment and counselling in women with cystinosis who plan to become pregnant (expert-based, strong consensus)
- We recommend stopping systemic cysteamine treatment as soon as the diagnosis of pregnancy is made (evidence-based, strong consensus)
- We recommend that patients resume cysteamine therapy as soon as possible after giving birth (expert-based, consensus)
- We do not suggest adjusting the dose of cysteamine in mothers who wish to breastfeed. However, we recommend discussing issues related to the unknown effects of potential cysteamine excretion in breast milk (expert-based, consensus)
- We do not recommend stopping ocular cysteamine treatment during pregnancy (evidence-based, strong consensus)

Box 8 | Management of neurological disease

- We recommend that people with cystinosis are evaluated yearly from the age of 3 years by a paediatric neurologist, a neurodevelopmental disabilities specialist or a similarly qualified professional for possible neurological, sensorimotor, cognitive, behavioural, educational and psychosocial problems (expert-based, strong consensus)
- We recommend timely occupational, physical and educational interventions, as indicated by the results of testing (expert-based, strong consensus)
- We do not recommend performing systematic neuroimaging in patients with cystinosis in the absence of clinical symptoms suggesting neurological involvement (unexplained headaches, papilloedema, new onset of seizures, symptoms suggesting stroke, new onset of focal neurological deficits) (expert-based, strong consensus)
- We suggest considering treatment with daily oral L-carnitine in patients with muscle weakness or with low free-carnitine serum levels, especially if overt Fanconi syndrome is present (evidence-based, strong consensus)
- We do not recommend treating patients with cystinosis with coenzyme Q10 supplements (evidence-based, strong consensus)
- We recommend involving neuromuscular specialists, pulmonologists, speech therapists, otorhinolaryngologists, physiotherapists and occupational therapists to initiate early intervention therapies as soon as muscular symptoms are observed (expert-based, strong consensus)
- We recommend performing spirometry testing every 2 years (more frequently, if needed) from the age of 5 years. Measurements should include the forced vital capacity and the forced expiratory volume in 1s (expert-based, strong consensus)
- We recommend informing all patients about the extent of their current muscle status (expert-based, strong consensus)
- We do not suggest physiotherapy for primary prevention without any muscular or motor developmental delay (evidence-based, strong consensus)
- We suggest early physiotherapy for secondary prevention in the presence of muscular weakness or motor development delay (evidence-based, strong consensus)
- We recommend encouraging all patients, even at very young age, to participate actively in physical exercise (expert-based, strong consensus)

have children, genetic counselling is indicated to discuss the need to screen the partner for possible *CTNS* variants, particularly in cases of consanguinity or if the two partners belong to a highly consanguineous population. If the partner carries a pathogenic variant, pre-implantation genetic diagnosis might be performed, or a prenatal diagnosis can be made on samples obtained by chorionic villus sampling or by amniocentesis.

Male infertility and testosterone substitution

Men with infantile nephropathic cystinosis and juvenile cystinosis usually have azoospermia. Owing to its rarity, no definitive information is available in male patients with ocular cystinosis. Most adult male patients are infertile. The degeneration of the male gonads is mostly caused by progressive accrual of cystine in the genital parenchyma. This accumulation affects both the somatic Sertoli cells in the seminiferous tubules and the testosterone-producing Leydig cells in the testicular interstitium^{157,158}. In addition, epididymal obstruction of the male reproductive tract probably contributes to the reduced semen quality^{157,158}. Although testicular degenerative damage can be delayed by cysteamine, it has not been possible to prevent it¹⁵⁹. Cryopreservation of semen in men might enable biological paternity, but this process is only successful in a minority of adolescents or young men because most patients have insufficient sperm in their semen. If attempted, cryopreservation should be proposed as early as possible to increase the chances of recovering viable samples. In the case of azoospermia, sperm retrieval by microscopic testicular sperm extraction (mTESE) might still be possible. This approach has been successfully performed in some patients with infantile nephropathic cystinosis and has enabled them to father children¹⁶⁰.

mTESE is more successful if patients have normal testosterone (>10 nmol/l) and inhibin B levels, without testosterone substitution.

Transplant status and patient age do not limit the indication for the mTESE procedure.

Male patients with cystinosis develop testosterone deficiency owing to progressive cystine accumulation in Leydig cells^{157,161}. Hypergonadotropic hypogonadism in patients with cystinosis usually develops after spontaneous puberty (Tanner stage IV–V)^{157,158}. Screening for hypogonadism before the end of puberty is probably inappropriate. Testosterone substitution improves sexual desire and sexual activity, depressive symptoms, anaemia, low muscle mass and low bone mineralization^{162–164}. Patients should be informed about the suppressive effect of testosterone on spermatogenesis. Dose adjustments are based on serum morning testosterone levels and treatment is safe if patients are appropriately monitored¹⁶². Monitoring haemoglobin levels and haematocrit is particularly important when using testosterone undecanoate given the risk of polyglobulia.

No guidelines are available for testosterone supplementation in people with cystinosis, but current evidence suggests that they can be treated according to the guidelines for hypogonadism treatment used in the general population¹⁶⁵ (Box 9).

Female fertility and breastfeeding

As the life expectancy and quality of life of women with cystinosis is improving, they increasingly consider becoming pregnant despite the need to stop cysteamine therapy, which is teratogenic. However, most patients have high-risk pregnancies. Factors that complicate pregnancies include CKD, transplant status and cystinosis-related complications, including Fanconi syndrome, cardiorespiratory dysfunction, hypothyroidism, diabetes mellitus and non-cirrhotic portal hypertension. Patients therefore need a comprehensive assessment, preferably before and during pregnancy, in a high-risk pregnancy clinic.

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Table 3 | Standardized diagnosis and therapy of feeding, swallowing and voice disorder

Symptoms	Examination ^a	Diagnosis	Therapy ^b
Children (0–12 years)			
Failure to thrive, weight loss, dehydration	Eating assessment tool (PEDI-EAT-10)	Avoiding restrictive food intake disorder (ARFID) or feeding disorder	Paediatric or gastroenterology treatment, including tube feeding
Recurrent infections	Oral motor skills	Sensory processing disorder (SPD)	ENT (including phoniatrics)
Gagging, coughing, vomiting	Assessment of swallow-relevant motor and sensory functions	Oral or oropharyngeal dysphagia	Speech and language therapy (SLT)
Lack of chewing and tongue movements	Observation of food intake	Gastroesophageal reflux disease (GERD)	Occupational therapy (OT)
Food getting stuck in the throat or oesophagus	Measurement of lip force		Psychological counselling
Extended mealtimes	Test of masticating and swallowing solids (TOMASS)		Parental advice
Avoiding certain foods, tastes and consistencies	Fibreoptic endoscopic evaluation of swallowing (FEES)		
Problems taking medication	Video fluoroscopy (VFS)		
	Ultrasound of tongue and oesophagus		
Adolescents (from 12 years) and adults			
Weight loss, dehydration	Eating assessment tool (EAT-10)	Oropharyngeal and/or oesophageal dysphagia	Speech and language therapy (SLT): individually tailored functional dysphagia therapy (restitutive, adaptive and compensatory therapeutic strategies); voice therapy; speech therapy
Recurrent infections or pneumonia	Dysphagia Handicap Index (DHI)	Oesophageal motility disorder (EMD)	Gastroenterology treatment: including early placement of feeding tube; ENT (including phoniatrics)
During the initial and further examinations, taking the medical history according to problems of swallowing (food, fluid, saliva, medication), voice problems and speech alterations	Sydney Swallow Questionnaire (SSQ)	Gastroesophageal reflux disease (GERD)	Neurologist
	Assessment of swallow-relevant motor and sensory functions; measurement of lip force	Dysphonia	
	Timed water test of swallowing (Daniels)	Dysarthria	
	Test of masticating and swallowing solids (TOMASS)		
	Fibreoptic endoscopic evaluation of swallowing (FEES)		
	Video fluoroscopy (VFS)		
	Ultrasound of tongue and oesophagus		
	Voice assessment, vocal quality of life questionnaire (for example, Voice Handicap Index (VHI) or short version (VHI-12))		

ENT, ear-nose-throat. ^aDependent on age and method availability. ^bDependent on diagnosis.

Before cysteamine treatment, individuals with cystinosis typically experienced hypotonia and poor motor coordination in early childhood, followed by progressive myopathy during adolescence and early adulthood. These conditions are still observed with cysteamine treatment, but to a much lesser degree and typically in older patients.

Muscle involvement in cystinosis is secondary to the accumulation of cystine crystals within the lysosomes of skeletal muscles, which leads to vacuolar myopathy, muscle fibre degeneration and muscle wasting^{143,144}. Electromyography usually shows a myopathic pattern^{36,145} and muscle biopsies might reveal vacuolar changes and sarcoplasmic inclusions¹⁴⁴. The severity of myopathy correlates with age and disease duration¹⁴⁶ and some studies indicate that it might also correlate with leukocyte cystine levels, although the evidence is inconsistent^{93,146–148}.

Cystinosis-associated myopathy typically begins in the hands and shoulders, and progresses centrally, prominently involving the oromotor and respiratory muscles¹⁴⁹. Patients might experience difficulties with chewing, swallowing, articulating and phonation (Table 3). At each clinic visit, adolescents and adults should be systematically evaluated for possible oromotor dysfunction (Supplementary Box 3). Individuals with advanced myopathy are at risk of choking, which can lead to aspiration pneumonia, as well as difficulties in coughing, clearing secretions and breathing. Some patients with advanced respiratory muscle involvement must use a continuous positive airway pressure device to guarantee adequate ventilation. Ultimately, this myopathy becomes a life-threatening condition. Studies are ongoing

to investigate the effectiveness of exercise in improving myopathy in patients with cystinosis. These studies include preventive interventions and exercises aimed at regaining muscle strength and improving oromotor function¹⁵⁰ (Table 3).

Carnitine is important for mitochondrial function, which is increasingly implicated in the pathogenesis of cystinotic tissue dysfunction, including muscle disease. Carnitine levels are decreased in the muscles of people with cystinosis, possibly owing to urinary losses caused by Fanconi syndrome^{151,152}. Serum carnitine levels (total, free acylcarnitines) should be measured annually from the age of 1 year. Oral levocarnitine (L-carnitine) supplementation can replenish muscle carnitine in these patients^{152,153} and should be the only compound used for carnitine supplementation. The initial dose is 25–100 mg/kg/day, divided into 2–3 daily doses. The dose should be decreased if levels rise above the reference values.

Of note, unlike in mitochondrial disorders^{154–156}, the effectiveness of L-carnitine in improving muscle strength has not yet been firmly demonstrated in cystinosis. Theoretically, coenzyme Q10 supplementation might also improve mitochondrial function but supporting studies are lacking (Box 8).

Fertility

Most male patients with infantile nephropathic cystinosis are infertile. Although most women are fertile, their fertility rate is lower than that of the general population, mostly because a substantial proportion of patients has CKD, and in part because of complications related to cystinosis. Whenever a patient with cystinosis wants to

Box 6 | Management of gastrointestinal involvement

- We recommend monitoring the nutritional status of patients with cystinosis at all ages, especially during the growth period (expert-based, strong consensus, additional recommendation)
- We suggest following the general recommendations on energy, macro- and micronutrient intake of the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in Children with Chronic Kidney Disease²¹² and the Clinical Practice Recommendations from the Paediatric Renal Nutrition Task force²¹³ in children with nephropathic cystinosis, as well as the Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in adult patients²¹² (expert-based, strong consensus)
- We recommend early diagnosis and treatment of gastrointestinal symptoms in patients with cystinosis (expert-based, strong consensus, additional recommendation)
- We recommend evaluating patients with cystinosis presenting with gastrointestinal symptoms for possible cysteamine toxicity (expert-based, strong consensus, additional recommendation)
- We suggest using proton pump inhibitors in patients who develop gastrointestinal symptoms, including nausea, vomiting, abdominal pain or gastroesophageal reflux (evidence-based, consensus)
- We recommend prevention, early detection and treatment of malnutrition in patients with cystinosis following international guidelines for children and adults (expert-based, strong consensus)

4–12 weeks is important to adjust the dose of thyroxine. Once stable thyroid-stimulating hormone levels have been obtained, monitoring can be extended to every 6–12 months, following the international guidelines for the treatment of hypothyroidism¹²⁴ (Box 7).

Diabetes mellitus

Many people with nephropathic cystinosis develop glucose intolerance and eventually diabetes mellitus^{4,125}. The diagnostic criteria are the same as those used for the general population¹²⁶. Of note, the accuracy of the glycated haemoglobin (HbA1c) level as a biomarker of hyperglycaemia declines in people with advanced CKD. General measures to prevent diabetes-related complications are the same as those used for the general population¹²⁷.

Some people with nephropathic cystinosis might also develop global pancreatic failure with overt exocrine pancreatic insufficiency. People with cystinosis and hyperglycaemia should always be evaluated for possible malabsorption, and glucose intolerance or diabetes mellitus should always be ruled out in those who develop steatorrhea or fat malabsorption.

Historical data from the late 1990s show that ~50% of patients with nephropathic cystinosis had glucose intolerance by 18 years of age^{125,128}. Cysteamine treatment delays and, in some patients, prevents the onset of diabetes, even if started after the age of 5 years²⁸. Subsequent data indicate reduced incidence and prevalence of diabetes mellitus in people with cystinosis¹²⁹. This change is most likely related to the increased availability

of cysteamine therapy in the past decades in Western countries and the implementation of steroid-sparing regimens for kidney transplantation.

In principle, kidney transplantation increases the risk of developing diabetes owing to the side effects of immunosuppressive therapies, especially tacrolimus and prednisone. However, data are conflicting^{88,128,130}. Of note, the incidence of post-transplant hyperglycaemia has clearly decreased with the adoption of steroid avoidance or steroid-sparing immunosuppressive protocols. Currently, 10–25% of transplant recipients in the general population develop diabetes mellitus, which is transient in most cases^{130,131} (Box 7).

Neurological and muscle involvement

People with cystinosis might develop neurocognitive, neuromotor and neuromuscular symptoms.

Neurocognitive complications are observed in ~50% of individuals and include deficits in visual–spatial, visual–motor, attention and executive functions^{132–137}. Cognitive and learning difficulties are also common in children with cystinosis. Many patients manifest these difficulties early in life, which can lead to academic and social struggles if not addressed in a timely fashion. Behavioural, cognitive and coordination issues, as well as balance problems, should be assessed from the age of 3 years, preferably by paediatric neurologists with neurodevelopmental training or similarly qualified individuals.

Despite the paucity of scientific evidence, anecdotal reports and one single study¹³⁸ indicate that the ability of children with cystinosis to learn can be improved by early identification of neurocognitive deficits and the implementation of academic and therapeutic interventions aimed at reducing their impact and maximizing learning. During adolescence, deficits in executive functioning might complicate medical treatment owing to impairments in understanding causes and effects, lack of organizational skills and other related issues. Adults sometimes require workplace adjustments to meet their needs.

Brain imaging performed in individuals with or without neurological symptoms shows several anomalies, including cortical and central volume losses, punctate hyperintensities, calcification of the basal ganglia and of the periventricular regions, or the presence of Chiari type I malformation¹³⁹. Both grey- and white-matter changes have been observed on quantitative analyses^{140–142}, but no evidence suggests that performing early neuroimaging influences the neurological outcomes of patients.

Box 7 | Management of endocrine involvement

- We recommend measuring thyroid-stimulating hormone and free thyroxine levels at least annually in all individuals with nephropathic cystinosis. In the case of abnormal findings, collaborative management with an endocrinologist should be established (expert-based, strong consensus)
- We recommend screening people with nephropathic cystinosis for glucose intolerance and diabetes mellitus by measuring fasting blood glucose and glycated haemoglobin levels at least annually, and more frequently in the immediate post-transplant period. In the case of abnormal findings, collaborative management with an endocrinologist should be established (expert-based, strong consensus)

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late, it can still be effective in protecting the thyroid gland^{28,35}. Typically, patients manifest with elevated thyroid-stimulating hormone and low free thyroxine levels during routine blood tests, when they are still asymptomatic. Monitoring the thyroid gland by ultrasound

examination might provide very early evidence of thyroid involvement, before hormonal changes become apparent¹²³. Patients should be started on thyroxine treatment immediately after confirmation of hypothyroidism. Close hormonal monitoring in the first

Box 5 | Monitoring and treatment of cystinosis metabolic bone disease

Clinical history

- History of musculoskeletal pain, bone fractures and deformities, orthopaedic interventions and muscle weakness

Physical examination

- Monitor bone deformities, signs of scoliosis, muscle strength and signs of muscle atrophy at every visit. Check for tenderness in bones due to rickets

Laboratory investigation

- Therapeutic decisions should be based on trends rather than single measurements

Biomarkers for cystinosis metabolic bone disease

- Calcium (Ca), phosphate, alkaline phosphatase (ALP) (bone-specific ALP in adults), parathyroid hormone, 25(OH) vitamin D, bicarbonate, and urinary calcium every 1 to 6 months with frequency of assessment based on age, chronic kidney disease (CKD) stage, and the presence and severity of cystinosis metabolic bone disease
- Ionized Ca levels. If this measurement is not available, use albumin-corrected calcium instead of total calcium in case of hypoalbuminaemia to detect hypocalcaemia. Measure markers of gonadal function every 12 months in adults

Treatment of cystinosis metabolic bone disease

- Vitamin D and calcium supplements should be used according to available recommendations for healthy individuals and people with CKD^{55,208,209}. Dose requirements might be initially higher. Serum 25(OH) vitamin D, Ca, phosphate, ALP and bicarbonate (HCO_3^-) should be kept within the normal range for age, although HCO_3^- levels of 22–26 mmol/l might not be achievable in all patients. Parathyroid hormone levels should be maintained within the target range for different CKD stages. Supplements might need to be adapted for interactions with other medications and in individuals with pancreatic exocrine insufficiency
- Vitamin D adheres to plastic materials. When administered through a naso-gastric or gastrostomy tube, the dose usually needs to be increased
- Hypophosphataemia requires oral phosphate supplementation. Increasing dietary intake of phosphate can be considered. Oral phosphate and calcium should be given separately. The usual starting dose is 20–40 mg (0.7–1.4 mmol)/kg/day based on elemental phosphorus divided in 3–5 doses. Thereafter, treatment should be individualized based on the clinical response. Treatment should be aimed at controlling osteomalacia and rickets (that is, normalizing ALPs) and not at normalizing serum phosphate. In some patients, ALP or bone-specific

ALP normalization is difficult. For the interpretation of serum phosphate and serum alkaline phosphatase levels, age-adapted reference values should always be used. Avoid doses of phosphate > 80 mg/kg/day

- Calcitriol or alfacalcidol are usually started at a dose of 10–20 ng/kg/day and 20–40 ng/kg/day, respectively. Alternatively, in patients aged > 1 year, a starting dose of 0.25 µg/day of calcitriol or 0.5 µg/day of alfacalcidol can be used and adjusted based on clinical response. Avoid doses of calcitriol > 0.75 µg and doses of alfacalcidol > 1.5 µg/day

Treatment with recombinant human growth hormone

- Monitor growth at least every 6 months, with more frequent assessments during periods of rapid growth. These include infancy (monthly assessments might be required) and puberty (growth should be checked every 3 months)
- Consider treatment with recombinant human growth hormone (rhGH) in children with persistent height below the 3rd percentile and a height velocity below the 25th percentile, after correcting for malnutrition, acidosis, hypothyroidism and hyperparathyroidism. Unlike children with CKD from other causes, rhGH can be considered in children with cystinosis who meet these criteria, even if they still have a normal estimated glomerular filtration rate
- Consider rhGH therapy 6 months to 1 year after transplantation in children with persistent growth failure, especially if steroid-free immunosuppression is not applicable
- Before starting treatment with rhGH, bone age should always be measured to ensure open epiphyses
- Use starting subcutaneous rhGH doses of 0.045–0.05 mg/kg/day in the evening. In Europe, yearly bone age evaluations in children receiving growth hormone are not recommended²¹¹, whereas routine annual X-rays are recommended in the USA

Orthopaedic interventions

- Patients with cystinosis frequently have foot deformities. Sensomotoric insoles can be prescribed if deformities are still flexible. Minimally invasive surgery should be preferred in patients who have not responded to conservative treatment
- Significant leg deformities might require surgery, including guided-growth techniques when treatment can be initiated more than 3 years before epiphyseal closure. After final skeletal maturation, osteotomies can be performed, if necessary
- If patients develop scoliosis, appropriate therapy should be initiated, including physiotherapy, corset, and/or surgery. Treatment of scoliosis is particularly important because patients with cystinosis are at risk of developing restrictive lung disease

Box 4 | Cystinosis bone disease

- We recommend following age-appropriate monitoring of cystinosis metabolic bone disease in people with cystinosis (Box 5) (expert-based, strong consensus)
- We recommend following age-appropriate treatment of chronic kidney disease (CKD)–mineral bone disorder, including correction of mineral metabolism, treatment with growth hormone, promoting physical activity, initiating physiotherapy and orthopaedic treatments (Box 5) (expert-based, strong consensus)
- We recommend following the general rules for CKD–mineral bone disorder^{65,206–209} management in people with CKD stages 4 and 5 (expert-based, strong consensus)
- We recommend combined phosphate and active vitamin D supplementation in people with Fanconi syndrome (expert-based, strong consensus)
- We recommend keeping serum 25(OH)-vitamin D concentrations within the target range of 75–150 nmol/l (30–60 ng/ml)²¹⁰ with ergocalciferol or cholecalciferol, as needed (expert-based, strong consensus)
- We recommend using the lowest dose of active vitamin D needed for effective treatment of rickets and osteomalacia (expert-based, strong consensus)
- We recommend prescribing oral calcium supplementation if appropriate nutritional calcium intake for age cannot be achieved (evidence-based, strong consensus)
- We suggest prescribing oral calcium supplementation if patients have hypocalcaemia, despite adequate 25(OH)-vitamin D and 1,25(OH)₂ treatment (evidence-based, strong consensus)
- We do not recommend performing systematic radiological evaluations (expert-based, strong consensus)
- We recommend performing plain X-rays in patients with a clinical suspicion of bone disease if results might influence clinical management (expert-based, strong consensus)
- We do not recommend performing routine dual energy X-ray absorptiometry, peripheral quantitative computed tomography or bone biopsy in patients with cystinosis (expert-based, strong consensus)

with cystinosis, depending on their age and clinical status. Given that no evidence is available for using a specific tool in cystinosis, physicians and health professionals should follow current guidelines. Proposed assessments tools include 3-day diet records, the Malnutrition Universal Screening Tool questionnaire, the seven-point Subjective Global Assessment questionnaire and the Patient-Generated Subjective Global Assessment questionnaire.

All patients should receive appropriate and balanced caloric intake according to age-specific reference daily allowances. For individuals who cannot meet their energy requirements, food fortification should be used; usually, high-energy products containing macro- and micronutrients are sufficient.

In addition, people with renal Fanconi syndrome require food with high-phosphate, high-potassium and high-sodium content. Dietary prescriptions should be guided by measuring urinary and serum electrolyte levels. In people with metabolic acidosis, reducing non-dairy animal protein intake, eating foods with high citrate

content and drinking bicarbonate-rich mineral water should be encouraged¹¹³.

In infants and young children, tube feeding is often necessary and can be achieved using a nasogastric tube, a percutaneous endoscopic gastrostomy, a gastric tube or a button gastrostomy. The decision to start tube feeding should not be postponed if adequate oral nutrition is not possible. Tube feeding also facilitates the administration of oral medications in small children. During tube feeding, osmotic diarrhoea can develop but decreasing the pump speed is usually sufficient to reduce the risk of diarrhoea. Adults with severe myopathy might also require tube feeding. General guidelines for tube feeding and handling of gastrostomies should be followed^{114–116}.

Some gastrointestinal symptoms improve with age – Fanconi syndrome tends to stabilize and oral supplements do not require systematic adjustments based on weight. However, in older individuals, progressive myopathy can impair swallowing and gastrointestinal motility, and patients can develop diabetes mellitus, which requires specific dietary adjustments^{109,117}.

Oral cysteamine increases gastrin serum levels and stimulates gastric acid secretion^{118,119}, with most patients experiencing gastrointestinal discomfort. PPIs are often prescribed to alleviate gastric symptoms¹¹⁹ and those patients should be monitored for side effects, including vitamin B12 deficiency, and prescriptions should be re-evaluated every 6 months. A stepwise discontinuation of PPIs should be considered after improvement of gastrointestinal symptoms.

Symptomatic patients might require cysteamine dose adjustments. Recent reports suggest that delayed-release cysteamine might be better tolerated from a gastrointestinal standpoint⁵². However, fibrosing colonopathy has been reported during the post-marketing surveillance of patients treated with delayed-release cysteamine. This condition should be suspected in patients who develop severe, persistent and/or worsening abdominal symptoms. The diagnosis requires performing a colonoscopy with colon biopsies. If confirmed, patients should be switched to the immediate-release formulation permanently. Overall, the evidence supporting routine use of PPIs and the use of delayed-release formulations to decrease gastrointestinal symptoms is limited.

In the post-transplant period, immunosuppressive therapies might also aggravate gastrointestinal symptoms. In patients with persistent vomiting, prescription of anti-emetic medication for a limited time might be appropriate⁹³. Chronic diarrhoea should always be reviewed and treated systematically to prevent dehydration, electrolyte disturbances and to guarantee appropriate caloric intake. Patients with cystinosis might also develop gastrointestinal symptoms owing to enteric infections, food intolerances, food allergies, inflammatory bowel disease or irritable bowel syndrome. These potential causes should always be considered (Box 6).

Endocrine diseases

Thyroid involvement

Hypothyroidism is the most frequent and usually the earliest endocrine dysfunction in cystinosis, particularly in patients with the infantile form. Thyroid dysfunction is caused primarily by inflammatory changes secondary to lysosomal cystine crystal accumulation in the gland parenchyma¹²⁰.

An estimated 50–75% of people with nephropathic cystinosis develop hypothyroidism at some point in their life^{121,122}. Cysteamine treatment can delay and possibly prevent the development of hypothyroidism. Cohort data suggest that even when therapy is started

Dialysis and kidney transplantation

No specific instructions for dialysis apply to people with cystinosis. Cysteamine therapy should not be discontinued. Renal Fanconi syndrome usually decreases in severity when patients are treated with dialysis and does not recur in the transplanted graft. Nephrectomy might be considered prior to kidney transplantation in patients with severe polyuria⁸⁷. Severe proteinuria requiring native kidney nephrectomy is rare. Usually, native kidney diuresis decreases rapidly after transplantation, but occasionally, post-transplant nephrectomy might be indicated.

Evaluation for kidney transplantation should include all known extra-renal complications of cystinosis. Kidney transplantation is usually successful with good long-term outcomes that are, on average, superior to those observed in people with other underlying kidney diseases^{88–92}. However, transplant recipients with cystinosis have significantly higher long-term morbidity owing to the extra-renal complications of their disease^{92,93}. Both living and deceased donor kidney transplants perform well and heterozygous relatives are acceptable donors. When possible, pre-emptive kidney transplantation should be prioritized. Limited cystine accumulation is observed in the interstitium of the kidney graft, which is repopulated with cells originating from the host. Exceptionally, patients with severe portal hypertension might require combined kidney and liver transplantation.

Cysteamine treatment should be restarted as soon as possible after transplantation⁹⁴ and does not interfere with the absorption and metabolism of current immunosuppressive drugs. The choice of immunosuppressive regimen depends on local protocols. In principle, the use of high doses of glucocorticoids and tacrolimus increases the risk of diabetes mellitus in people with cystinosis, who are prone to developing endocrine pancreatic insufficiency. Whether these considerations should modify the immunosuppressive approach is debatable (Box 3).

Bone disease

Cystinosis metabolic bone disease (CMBD) is associated with high morbidity and reduced health-related quality of life (HR-QoL)^{95–97} (Fig. 2). Individuals with nephropathic cystinosis usually develop growth failure during the first 2 years of life. Short stature often becomes disproportionate during the 2nd year of life because growth of the lower limbs is more severely impaired than growth of the trunk segment. Signs of rickets and osteomalacia include bone pain, thickening and widening of the wrists and ankles, waddling gait, leg deformities, scoliosis, low bone mineral density and bone fractures^{98–102}. Some patients require orthopaedic interventions to improve mobility. Individuals with nephropathic cystinosis are also at risk of developing progressive distal myopathy, which is initially subclinical. Decreased muscle strength impairs the 'bone–muscle unit', aggravating bone hypomineralization.

The pathophysiology of CMBD is multifactorial, including hypophosphataemic rickets and osteomalacia, metabolic acidosis, hypercalciuria, mineral and bone disorder due to CKD (CKD–MBD)^{95,102–105}, malnutrition, muscle wasting, endocrine disorders (for example, hypogonadism or hypothyroidism) and an intrinsic bone defect secondary to lack of *CTNS* function in bone cells⁹⁷ (Supplementary Box 2).

Treatment of CMBD usually requires phosphate, calcium, vitamin D supplementation and/or treatment with active vitamin D. In these patients, yearly kidney ultrasound is necessary to monitor the potential development of nephrocalcinosis (Boxes 4 and 5).

Gastrointestinal involvement and malnutrition

Malnutrition is multifactorial and is highly prevalent in people with cystinosis^{106–109}. Patients often have poor appetite secondary to the high fluid and salt intake required to compensate for urinary losses, as well as the gastrointestinal discomfort caused by cysteamine therapy. Patients complain very frequently of nausea, vomiting and diarrhoea^{106–109}. They also frequently complain of abdominal pain, bloating and, more rarely, of severe dyspepsia related to gastric ulcers^{106–109}. Chronic inflammation and CKD further aggravate the nutritional status¹¹⁰. Most patients have low body mass index (BMI) and reduced muscle mass¹¹¹. They require individualized dietetic management to guarantee optimal nutritional intake.

The Global Leadership Initiative on Malnutrition (GLIM) criteria also apply to adults with cystinosis¹¹². All patients should be evaluated following a structured diagnostic scheme¹¹². An integrated approach with a team of nephrologists, gastroenterologists, dietitians, speech therapists, occupational therapists, physiotherapists and psychologists is often required.

The assessment of food intake, nutritional status and gastrointestinal health should be performed at regular intervals for all patients

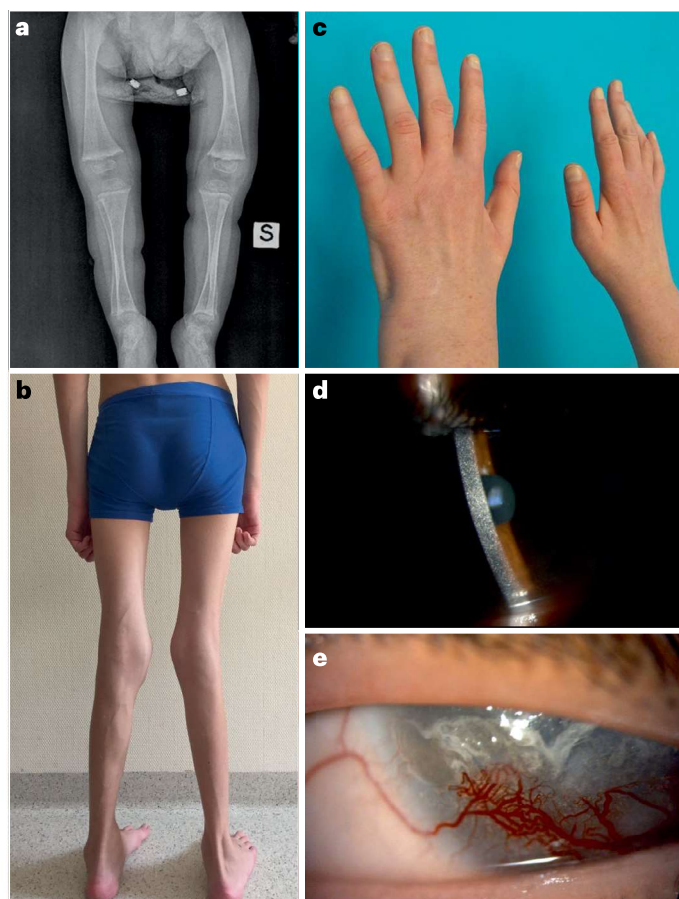


Fig. 2 | Clinical features of patients with infantile nephropathic cystinosis. **a**, X-ray of the lower limbs of an infant with overt rickets secondary to Fanconi syndrome. **b**, Genu valgum and limb asymmetry in an adolescent male patient. **c**, Hand muscle wasting in an adult patient with cystinosis-related myopathy. **d**, Corneal cystine crystal depositions (slit-lamp examination). **e**, Corneal neovascularization and band keratopathy in a patient without adequate cysteamine eye-drop treatment.

Box 3 | Treatment of kidney disease

- We recommend regular monitoring of glomerular and tubular function in all people with nephropathic cystinosis by a paediatric or adult nephrologist with experience in the treatment of patients with nephropathic cystinosis (expert-based, strong consensus)
- We recommend monitoring electrolyte and serum bicarbonate levels regularly, at least every 2–3 months in small children; in children older than 6 years, monitoring can be extended to 3–4 months if patients have a stable clinical condition (evidence-based, strong consensus)
- We recommend adjusting the dose of sodium, chloride, phosphate, calcium, potassium and magnesium supplements to maintain serum levels within the normal range (evidence-based, strong consensus)
- We recommend adjusting the dose of potassium supplements to maintain serum levels ≥ 3 mmol/l, similar to the recommendations for other hypokalaemic genetic tubular diseases (expert-based, strong consensus)
- We recommend alkali supplementation to achieve through serum bicarbonate levels ranging between 22–26 mmol/l (expert-based, strong consensus)
- We recommend administering alkali supplements (bicarbonate- or citrate-based) in 3–4 daily doses, unless delayed-release formulations are available (expert-based, strong consensus)
- We recommend guaranteeing free access to water and restrooms to all patients with polyuria and polydipsia secondary to renal Fanconi syndrome (expert-based, strong consensus, additional recommendation)
- We suggest treating children with polyuria and uncontrolled Fanconi syndrome with indomethacin or other NSAIDs (evidence-based, consensus)
- We suggest stopping NSAIDs treatment as soon as renal Fanconi syndrome can be controlled with oral supplements (expert-based, consensus)
- We do not recommend using NSAIDs in older children and adults with impaired kidney function (expert-based, consensus)
- We recommend stopping NSAIDs in patients with declining kidney function (expert-based, consensus)
- We recommend not using NSAIDs in combination with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), or combining two different NSAIDs (expert-based, strong consensus)
- We do not recommend the routine use of ACE inhibitors or ARBs for nephroprotection in people with nephropathic cystinosis (evidence-based, consensus)
- We suggest considering using ACE inhibitors or ARBs in people with overt glomerular proteinuria and/or hypertension (expert-based, consensus)
- We recommend performing kidney transplantation in patients with advanced chronic kidney disease or kidney failure secondary to cystinosis; if possible, pre-emptive transplantation should be preferred (expert-based, strong consensus)
- We recommend starting haemodialysis or peritoneal dialysis following current guidelines if transplantation is not available or contraindicated (expert-based, strong consensus)
- We suggest considering nephrectomy prior to kidney transplantation in patients with severe polyuria and/or proteinuria (expert-based, strong consensus)

acidosis⁷⁶) and expert opinion indicate a clear benefit in providing alkali, electrolyte and fluid supplementation. Nasogastric tube or gastrostomy tube placement might be needed to guarantee appropriate fluid and electrolyte administration in infants and children, in addition to medications and nutrition (see the section on Gastrointestinal involvement and malnutrition). The choice of alkali supplement depends on availability, age-adapted formulations, kidney function and cost. Patients are treated with sodium- or potassium-based bicarbonate or citrate solutions, capsules or tablets. Commercially available baking soda for human use is cheap and can be safely prescribed when bicarbonate tablets or solutions are not available (for example, 1 tablespoon equals ~4.8 g of sodium bicarbonate and provides 59 mmol of bicarbonate and sodium). Three historical small case studies suggested that hydrochlorothiazide might help to treat metabolic acidosis in combination with alkali therapy^{77–79}. Currently, the evidence is too weak to recommend the systematic use of hydrochlorothiazide, but this drug can be used when metabolic acidosis cannot be controlled with alkali supplements.

Treatment with indomethacin (1–3 mg/kg/day divided into 2–3 doses) and, less frequently, with other NSAIDs, is aimed at reducing tubular water and electrolyte losses, and improving growth and metabolic stability^{80,81}. However, the evidence favouring the prescription of NSAIDs in cystinosis remains inconclusive^{35,82}. Side effects include gastrointestinal symptoms and possibly nephrotoxicity. Usually, these effects are not observed in small children unless very high doses are

prescribed. Co-treatment with PPIs decreases the risk of associated gastrointestinal side effects. Although indomethacin might be helpful in reducing enuresis, evidence to support its use for this purpose is lacking.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are known to attenuate progression to kidney failure in people with CKD, especially in those with proteinuric podocytopathies^{83,84}. Current guidelines recommend the use of ACE inhibitors or ARBs in all people with CKD and proteinuria or hypertension^{85,86}. In cystinosis, these drugs should be prescribed with caution because they might cause hypotension and worsen kidney function in hypovolaemic patients. Currently, no clear evidence demonstrates that ACE inhibitors or ARBs can mitigate kidney function deterioration in cystinosis. However, some patients can develop severe albuminuria (that is, urinary albumin-to-creatinine ratio > 1 mg/mg), presumably partly owing to glomerular dysfunction, and might benefit from treatment with these drugs.

Given that NSAIDs, ACE inhibitors and ARBs decrease glomerular perfusion, combining these therapies is not recommended in people with CKD. These drugs should also be discontinued during episodes of dehydration and NSAIDs should be stopped when kidney function is substantially compromised. Although no established thresholds exist, NSAIDs should probably not be used in people with CKD stage ≥ 3 . Sodium–glucose co-transporter 2 (SGLT2) inhibitors are efficient in decreasing progression of CKD in other forms of kidney disease, but data in people with cystinosis are lacking (Box 3).

Consensus statement

Table 2 | Proposed weight-adjusted doses of immediate-release cysteamine

Weight	Immediate-release cysteamine	Delayed-release cysteamine
<10 kg	80–85 mg/kg/day	65–70 mg/kg/day
10–17 kg	80 mg/kg/day	65 mg/kg/day
17–25 kg	70 mg/kg/day	55 mg/kg/day
25–40 kg	60 mg/kg/day	50 mg/kg/day
40–70 kg	50 mg/kg/day	40 mg/kg/day

Cysteamine is a sulphhydryl compound with a free thiol moiety that results in a bad odour and taste. Both cysteamine preparations have similar side effects, including foul odour, gastric discomfort, nausea and vomiting^{54–56}. Cystagon® and Procysbi® should be given every 6 h and every 12 h, respectively. Oral cysteamine is a major contributor to the gastrointestinal discomfort that often limits adherence^{57,58}. Adherence to cysteamine therapy can drop to as much as 50% in adulthood⁵⁹. The delayed-release formulation might increase treatment adherence and is often preferred by adolescent and adult patients^{60,61}.

The optimal dose of cysteamine varies. The recommended dose of immediate-release cysteamine bitartrate is 60–90 mg/kg/day or 1.3–1.95 g/m²/day divided into four doses administered every 6 h, according to the manufacturer's instructions. The recommended dose for the extended-release formulation is 80% of the immediate-release dose, divided into two doses and administered every 12 h. When beginning treatment, cysteamine should be started at a low dose and increased progressively. Typically, Cystagon® is started at 10 mg/kg/day and increased over a period of 6 weeks to reach the final therapeutic dose⁶². If well tolerated, dosage can be increased more rapidly. An optimized scheme for reaching appropriate cystine depletion using weight-adjusted doses has been reported⁶³ (Table 2).

The gastrointestinal side effects of cysteamine can be reduced by taking it with meals and, in some patients, by combining it with the use of proton pump inhibitors (PPIs). The foul odour and halitosis can be mitigated with chlorophyll tablets, zinc mouth wash or chewing gum containing zinc. Patients complaining of persistent headache with malaise should always be investigated to exclude pseudotumour cerebri (also known as idiopathic intracranial hypertension), although a causative association between cysteamine and pseudotumour cerebri has not been established. Exceptionally, patients might develop bruise-like lesions or striae rubrae that are possibly related to excessively high doses of cysteamine⁵⁴ and/or copper deficiency⁶⁴.

The cysteamine dose should be reduced in all patients with substantial side effects. In centres where measurement of leukocyte cystine levels is not available, the dose can be adapted based on clinical tolerance, as long as it does not exceed 90 mg/kg/day or 1.95 g/m²/day, with a maximal dose of 2.0 g/day, according to the manufacturer's instructions. Whenever possible, doses should be adjusted based on trough leukocyte cystine levels. In principle, the lowest possible leukocyte cystine level should be aimed for, within the dose limits specified above. However, in some centres, the dose of cysteamine is increased up to 3.6 g/day when adult patients cannot achieve adequate leukocyte cystine levels.

Cystine depletion should be measured 6 h after the last dose with immediate-release cysteamine and 12 h after the last dose with delayed-release cysteamine. Samples should be shipped according to specific laboratory protocols and results should be interpreted using

the reference values of individual laboratories. In the case of unexpected abnormal levels, measurements should be repeated before making substantial changes to the treatment dosage. Cystine levels should be assessed frequently (monthly) when starting therapy and every 3–6 months afterwards. Measurements should always be performed in the same laboratory to compare results over time.

Cysteamine is teratogenic and should be stopped during pregnancy (see the section on Fertility). The use of cysteamine eye drops is discussed later (Box 2).

Kidney disease and kidney transplantation

The recommendations for managing CKD, dialysis and kidney transplantation in the general population also apply to people with cystinosis^{65,66}.

Renal Fanconi syndrome and glomerular disease

Infantile nephropathic cystinosis is the most common cause of renal Fanconi syndrome in children. Tubular dysfunction causes polydipsia, polyuria, electrolyte disturbances and metabolic acidosis^{1,67–69}. Severe polydipsia can affect nutrition and calorie intake. Although proteinuria is initially tubular in origin, podocyte dysfunction and subsequent podocyte loss cause progressive glomerular proteinuria⁷⁰. Together with the worsening of tubular lesions, these effects can lead to increased proteinuria over time⁷¹. Current evidence suggests that tubular damage, once established, is irreversible^{72,73}, but very early initiation of cysteamine treatment (within 2 months of life) can prevent the development of severe renal Fanconi syndrome²⁶.

No controlled studies are available to inform the optimal management of Fanconi syndrome. Evidence from clinical practice, including observations in patients with other tubular disorders (for example, X-linked hyphosphataemia⁷⁴, Bartter syndrome⁷⁵ or distal renal tubular

Box 2 | Systemic treatment with cysteamine

- We recommend starting oral cysteamine therapy in individuals with cystinosis as soon as a diagnosis is made. Systemic cysteamine therapy should be prescribed to all patients with infantile nephropathic cystinosis or with juvenile cystinosis, at any age, and regardless of kidney function and transplant status (evidence-based, strong consensus)
- We do not recommend one specific formulation of cysteamine bitartrate over another (evidence-based, consensus)
- We recommend choosing a cysteamine formulation based on the needs of the patient needs and its availability (evidence-based, strong consensus)
- We do not suggest adjusting the dose of cysteamine based on kidney function in patients with advanced kidney failure or treated with dialysis²⁰⁵ (expert-based, strong consensus)
- We recommend resuming cysteamine treatment as soon as possible after kidney transplantation without dose adjustments (expert-based, strong consensus, additional recommendation)
- We recommend that patients who have interrupted treatment for any reason resume therapy as soon as possible with the same dose, unless they have interrupted cysteamine for more than 1 month; in that case, cysteamine should be re-started at a lower dose and increased progressively⁶² (expert-based, strong consensus, additional recommendation)

Consensus statement

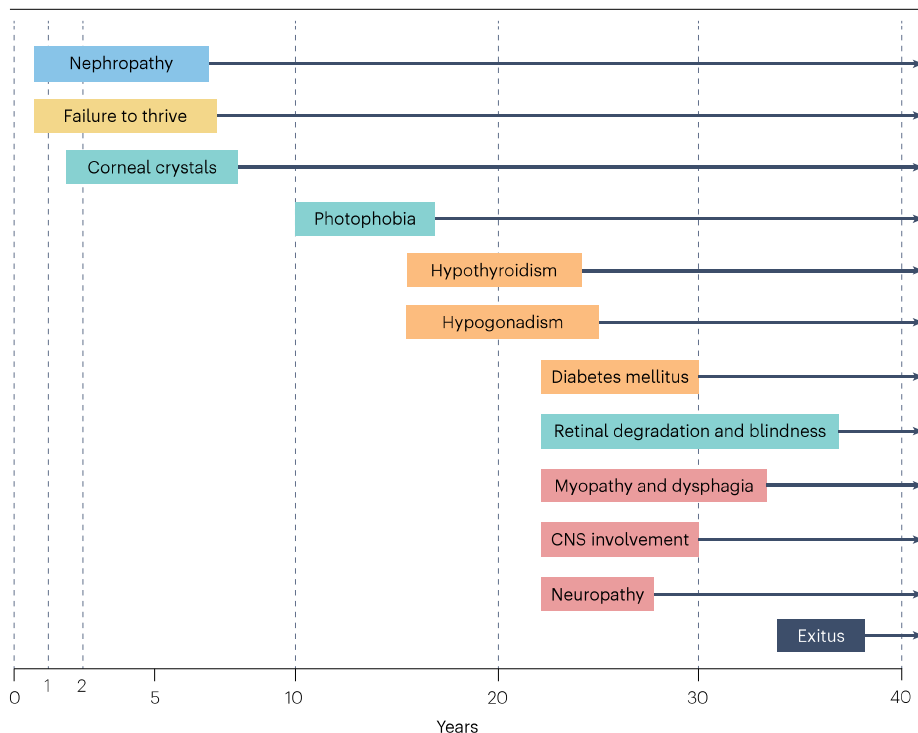


Fig. 1 | Indicative chronology of complications in patients not treated or poorly treated with cysteamine. Patients with infantile nephropathic cystinosis who are not treated with cysteamine typically develop Fanconi syndrome by 1 year of age, at which point and they would also exhibit failure to thrive; some children might already have some degree of chronic kidney failure. The second most frequent symptom is the deposition of corneal cystine crystals, which usually develop in the 2nd year of life. Significant inter-patient variations exist. Scale is not linear. Modified with permission from ref. 204, Elsevier. CNS, central nervous system.

cystine levels are also useful for monitoring cysteamine treatment⁴⁸, although they only reflect the effectiveness of treatment in the previous 24–48 h (see the section on cysteamine treatment below); therefore, assessment of treatment efficacy and adherence requires repeated measurements.

In some regions, genetic testing and cystine measurements are not available. In such circumstances, the presence of corneal cystine crystals in a child with renal Fanconi syndrome is sufficient for a cystinosis diagnosis, with the caveat that corneal crystals might not be present or might be hard to detect before the age of 2 years³⁷.

Three retrospective cohort studies showed that starting cysteamine treatment within the first 2 months of life, before the onset of clinical symptoms, attenuates renal Fanconi syndrome very significantly and preserves glomerular function during childhood^{24–26}. These observations provide a strong rationale for establishing newborn screening programmes. When an older sibling is affected, newborns should be tested immediately after birth. Of note, glycosuria is nearly always present after Fanconi syndrome has developed. However, the sensitivity and specificity of glycosuria are not sufficient to recommend its assessment as a screening tool for cystinosis. No other appropriate biochemical markers for screening are available. Molecular-based newborn screening is feasible and effective^{49,50}, providing strong evidence for including CTNS in molecular-based newborn screening panels (Box 1).

Cysteamine treatment

The only specific systemic treatment for nephropathic cystinosis is oral cysteamine, which is available in immediate-release (cysteamine bitartrate, Cystagon®) or delayed-release (Procysbi®) formulations. Both options have been approved by the FDA and the EMA, and are effective in lowering leukocyte cystine levels^{29,51–53}. When cysteamine treatment is started early, kidney function is significantly preserved

and kidney failure rarely occurs before the age of 20 years^{24,25,35}. In addition, the Fanconi syndrome can be significantly mitigated if treatment is started very early, within the first 2 months of life²⁶.

Box 1 | Clinical symptoms and diagnosis of cystinosis

- We recommend that cystinosis should be suspected if individuals present with typical clinical symptoms and laboratory findings (Table 1) (expert-based, strong consensus)
- We recommend a specific diagnostic work-up to confirm the diagnosis (Supplementary Table 1) (expert-based, strong consensus)
- We recommend measuring leukocyte cystine levels for diagnosing cystinosis, if available (expert-based, strong consensus)
- We recommend using either pure granulocyte or mixed leukocyte extracts to measure cystine levels. We suggest using preferably pure granulocytes, if available (expert-based, strong consensus)
- We suggest performing a slit-lamp eye examination in every child with a suspected diagnosis of cystinosis, taking into account that cystine crystals might not be present or be hard to detect before 2 years of age (expert-based, strong consensus)
- We recommend performing prenatal or immediate postnatal testing in all individuals at risk (expert-based, strong consensus)
- We recommend establishing newborn screening programmes for cystinosis (evidence-based, strong consensus)
- We do not recommend using glycosuria as a screening test for cystinosis in infants up to 3 months of age (expert-based, consensus)

Table 1 | Cystinosis disease subtypes

Disease subtype	Clinical symptoms	Laboratory findings and additional evaluation
Infantile nephropathic cystinosis (onset ~6 months)	Failure to thrive, lack of appetite (feeding difficulties), vomiting, polyuria, polydipsia, episodes of severe dehydration and unexplained fever (clinical signs of Fanconi syndrome), constipation and sometimes rickets, failure to walk, growth retardation and tetany	Electrolyte imbalance (hypokalaemia, hypophosphataemia, hypocalcaemia), metabolic acidosis and urinary loss of electrolytes, minerals and other small molecules (sodium, potassium, bicarbonate, calcium, phosphate, magnesium, glucose, amino acids, carnitine and proteins (α1-microglobulin)) as signs of renal tubular Fanconi syndrome
Juvenile cystinosis (onset in adolescence and early adulthood)	Chronic kidney disease with incomplete renal Fanconi syndrome and proteinuria; photophobia can be present	Mild disturbance of serum electrolytes as mild hypokalaemia, hypophosphataemia, metabolic acidosis, abnormal kidney function parameters (for example, GFR, creatinine, cystatin C), increased urinary excretion of electrolytes and minerals (sodium, potassium, bicarbonate, calcium, phosphate, magnesium), glucose, amino acids, tubular proteins (α1-microglobulin, β2-macroglobulin) and glomerular proteinuria (albuminuria), detection of corneal crystals on slit lamp examination Crystals should be present by the time intermediate nephropathic cystinosis is suspected
Ocular cystinosis (onset in adulthood)	Photophobia and/or crystals on slit-lamp examination	Slit-lamp examination to detect cornea crystals Examination for kidney involvement (for example, tubular or glomerular proteinuria or decreased GFR)

GFR, glomerular filtration rate.

Nephrology Association. The CPRs have also been supported and endorsed by the following German societies: Society for Paediatric Nephrology, German Federal Association for Speech and Language Therapy, German Society of Qualified Nutrition Therapists and Nutrition Consultants, German Society of Andrology, German Society of Endocrinology, German Society for Gastroenterology, Digestive and Metabolic Diseases, German Society of Human Genetics, German Society for Paediatric Endocrinology and Diabetology, German Society for Paediatrics and Adolescent Medicine, German Society for Clinical Chemistry and Laboratory Medicine, German Society for Medical Psychology, German Society of Nephrology, German Society for Newborn Screening, German Society for Orthopaedics and Trauma Surgery, German Interdisciplinary Society for Dysphagia, German Ophthalmological Society, German Association of Occupational Therapy, German Association for Physiotherapy, Society for Neuropediatrics, Society for Neuropsychology, and the Society for Paediatric Pulmonology.

Clinical symptoms and diagnosis of cystinosis

Cystinosis is a monogenic disease that manifests in three different clinical forms (Table 1).

Most patients have infantile nephropathic cystinosis – they are asymptomatic at birth and usually develop symptoms related to renal Fanconi syndrome in the first year of life. Most patients in Europe are diagnosed within the first 2 years of life³⁵. Symptoms include polyuria, polydipsia, dehydration, failure to thrive, vomiting, feeding difficulties, growth retardation and signs of rickets³⁶. From a metabolic standpoint, patients frequently have electrolyte disturbances, metabolic acidosis, hypophosphataemia and elevated bone-derived alkaline phosphatases. Without cysteamine treatment, the disease progresses to kidney failure at the age of around 10–12 years²⁷ (Fig. 1). By 2 years of age, cystine crystals can be observed in the cornea, causing progressive photophobia³⁷.

Juvenile or late-onset cystinosis is observed in ~5% of cases and is characterized by mild clinical and biochemical signs of proximal tubulopathy, which usually delays diagnosis³⁸. Patients are often diagnosed in adolescence after developing CKD or because they complain of photophobia. Corneal cystine crystals are always present after the

age of 2 years. Without treatment, these patients progress to kidney failure, but usually not until their late teens to mid-twenties³⁸.

Ocular cystinosis is extremely rare. Patients accumulate cystine crystals in their cornea, causing photophobia, without overt signs of systemic disease³⁹. In some cases, proteinuria and mild kidney disease develop in adulthood. Therefore, urine analysis and calculation of estimated glomerular filtration rate are always recommended for these patients.

Lysosomal cystine accumulation is observed in all patients with cystinosis and, in some cases, determining which of the three forms is present can be difficult. Cystinosis can be diagnosed through molecular genetic analysis showing biallelic pathogenic or likely pathogenic *CTNS* variants⁴⁰, detection of increased leukocyte cystine levels⁴ and ophthalmological examination of the anterior segment of the eye (usually by slit-lamp examination) showing cystine crystals in the cornea³⁷, which are usually absent or hard to detect in the first year of life (Supplementary Table 1). The diagnosis can also be made prenatally through genetic testing³⁶.

Genetic testing and leukocyte cystine levels are precise methods with a high diagnostic yield. Rarely, individuals with a suggestive clinical or biochemical phenotype require additional studies, including RNA⁴¹ or intronic sequencing. Occasionally, patients with low initial leukocyte cystine levels have been described⁴². In these individuals, fibroblast cultures might be needed to demonstrate increased lysosomal cystine accumulation⁴². After the age of 2 years, all patients with cystinosis have corneal cystine crystal depositions, confirming the diagnosis³⁷.

Cystine can be measured in mixed leukocyte or pure granulocyte samples⁴³. However, even in very experienced laboratories, results can vary significantly, mostly owing to issues during the pre-analytic phase, including sample preservation and/or sample shipment, leukocyte extraction, preservation of cell survival, cell sonication and protein measurements⁴⁴. Lysosome content varies in different leukocyte sub-populations. Granulocytes, which are rich in lysosomes, have a higher cystine content than lymphocytes⁴⁵. Thus, the leukocyte composition influences cystine determination when using mixed leukocyte samples⁴⁶. Measurements require highly standardized protocols that have been developed in specialized laboratories⁴⁷. Leukocyte

Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disorder with an estimated incidence of 0.5–1 in 100,000 live births¹. The disease is caused by biallelic pathogenic variants in *CTNS*, which is located on chromosome 17p13 and encodes cystinosisin, a lysosomal cystine–proton symporter². Over 170 pathogenic *CTNS* variants have been identified, including deletion, nonsense and frameshift variants, reflecting significant genotypic diversity across different populations and geographic regions³. Genotype–phenotype correlation in cystinosis is limited but hypomorphic partially functional variants might result in milder disease manifestations^{4–8}. The most common form of the disorder, termed infantile nephropathic cystinosis (OMIM 219800), is observed in 95% of cases¹. An intermediate form, termed juvenile or ‘late-onset’ cystinosis (OMIM 219900) represents 5% of cases¹. Ocular cystinosis (OMIM 219750) is exceptionally rare and is characterized by isolated corneal cystine crystal deposits without other substantial systemic manifestations¹. The most prevalent pathogenic variant in Northern Europeans is a 57 kb deletion^{9–11} spanning exons 1–10 of *CTNS*, *CARKL* and part of the adjacent *TRPVI*. This deletion accounts for ~50–70% of disease-causing alleles in patients of Northern European descent^{3,9,12} but is very rare in the Middle East, Asia and Southern Europe^{3,7,13,14}.

Loss of cystinosisin function disrupts lysosomal cystine efflux, resulting in lysosomal cystine accumulation and crystallization, which progressively cause multiorgan damage. Cystine accumulation is particularly detrimental to the kidneys, usually leading to renal Fanconi syndrome within the first year of life, which is characterized by clinical and biochemical evidence of proximal tubular dysfunction, followed by progressive chronic kidney disease (CKD)¹⁵. The pathogenesis of renal Fanconi syndrome is complex and includes, in addition to cystine accumulation, decreased availability of cytosolic cysteine, mechanistic target of rapamycin (mTOR) dysregulation, increased mitochondrial autophagy and mitochondrial damage, and increased oxidative stress^{16,17}. Cystinosisin can interact with numerous proteins, including components of the vacuolar H⁺-ATPase–Regulator–Rag complex, which is involved in mTOR complex 1 (mTORC1) signalling^{18–20}.

The introduction of cysteamine therapy in the 1970s and 1980s was a pivotal moment that changed the prognosis of the disease considerably²¹. Cysteamine is an aminothiol that depletes lysosomal cystine through reduction of cystine into cysteine and the formation of a cysteamine–cysteine mixed disulfide that can exit lysosomes via the PQLC2 cationic amino acid transporter^{22,23}. Currently, cysteamine remains the only specific treatment for cystinosis.

Very early initiation of cysteamine therapy is essential for preserving kidney function and optimizing long-term outcomes^{24–26}. Onset and severity of extra-renal complications – such as endocrine dysfunction, neuromuscular impairment or retinal degeneration – are closely linked to adherence to cysteamine therapy^{4,27–29}. The current generation of middle-aged adults with cystinosis is the first generation of patients who have benefited from early treatment with cysteamine after diagnosis. Long-term data, which are needed to fully appreciate the impact of this early treatment, will be available shortly.

In this Consensus Statement, we provide evidence-based and expert opinion-based clinical practice recommendations (CPRs) for the diagnosis, management and long-term care of people with cystinosis to support health care professionals, patients and families navigating the complexities of this lifelong disorder³⁰. Based on this text, patients and their caregivers have written a lay summary of these recommendations that incorporates their views and priorities (Supplementary Box 1).

Methods

This work was supported by the German Government (Innovation Fund, 01VSF22003) and followed guideline standards of the German Institute for Medical Knowledge Management³¹. The recommendations were developed by a team of international experts from different medical fields and societies, patient representatives and members of the Austrian Department for Evidence-based Medicine and Evaluation (University for Continuing Education Krems, Austria). All participants were required to disclose potential conflicts of interest, which were reviewed by an independent committee. Participants were excluded from voting on specific patient population, intervention, comparator and outcomes (PICO) questions and their grading, if relevant conflicts of interest were identified.

From a methodological standpoint, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was adopted. Briefly, the [GRADE framework](#) provides a structured process that includes the formulation of PICO questions, the definition and ranking of relevant outcomes, the screening of current literature, the elaboration of Evidence-to-Decision tables, and the formulating and justification of recommendations. Recommendations are based on evidence from literature, expert opinion and patient opinion. The assessment of the literature according to the GRADE framework requires assessing the risks of biases, data inconsistency, use of indirect strategies for data analyses and assessing data imprecision. This approach is particularly relevant when assessing older studies that did not follow stringent methodologies as outlined in the Consolidated Standards of Reporting Trials guidelines³², for example, and studies on rare diseases, which are usually underpowered.

The systematic review was performed by the Department for Evidence-based Medicine and Evaluation (University for Continuing Education Krems, Austria) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses³³ and [Cochrane guidelines](#). Detailed assessments of the PICO questions related to these CPRs and the corresponding levels of evidence are available elsewhere³⁴.

Recommendations were classified as strong (written in the text using the following wording: “we recommend” or “we do not recommend”), or standard or conditional recommendations (written in the text using the following wording: “we suggest” or “we do not suggest”). The strength of the consensus was defined according to the percentage of agreement among experts: “strong consensus”: agreement ≥ 95%; “consensus”: agreement ≥ 75%–95%; “no consensus”: agreement < 75%.

The CPR development process began in October 2022 and required 20 online meetings of the steering committee, 45 online meetings of working groups, 10 online meetings with all guideline participants and one final consensus meeting in person in April 2024 in Salzburg, Austria, under the moderation of the German Institute for Medical Knowledge Management. 18 working groups were created, addressing 31 PICO questions and 15 non-PICO questions. Six additional recommendations, which were included as comments in the ETD tables of the German version, are presented as a recommendation in the English version for clarity. A separate vote was taken by the entire group to validate these recommendations, following the same procedure used for the other CPRs.

The CPRs have been supported and endorsed by the following European and International societies: the International Paediatric Nephrology Association, the Asian Paediatric Nephrology Association, the Australian and New Zealand Paediatric Nephrology Association, the European Society for Paediatric Nephrology, the Japanese Society for Paediatric Nephrology, and the Latin American Paediatric

Clinical practice recommendations for the diagnosis and management of nephropathic cystinosis

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Abstract

Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in *CTNS*, which encodes cystinosin, a H⁺/cystine symporter that mediates cystine efflux from lysosomes. Defective cystinosin leads to accumulation of cystine in lysosomes and the formation of cystine crystals in most tissues. In its more severe and frequent form, infantile nephropathic cystinosis, patients present with renal Fanconi syndrome in the first 2 years of life, which progresses to chronic kidney disease. Since the 1970s, cysteamine therapy and improvements in dialysis and transplantation have substantially improved patient outcomes, and currently most patients survive into adulthood. Consequently, the diagnosis and management of extra-renal complications that develop later in life have become increasingly important. In addition to the kidneys, commonly affected organs include the eyes, the musculoskeletal system, the central nervous system, exocrine glands and endocrine organs. Cystinosis therefore requires integrated care that involves multiple medical specialties and a structured transition plan from paediatric to adult care. Herein, we present evidence-based and expert opinion-based clinical practice recommendations, developed by a team of international specialists and patient representatives following the GRADE methodology, to improve the diagnosis and management of cystinosis in children and adults.

Sections

Introduction

Methods

Clinical symptoms and diagnosis of cystinosis

Cysteamine treatment

Kidney disease and kidney transplantation

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Gastrointestinal involvement and malnutrition

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Psychosocial needs, transition and integrated care

Conclusion

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