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Consensus statement

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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

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Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disorder with an estimated incidence of 0.5–1 in 100,000 live births[1]. The disease is caused by biallelic pathogenic variants in *CTNS*, which is located on chromosome 17p13 and encodes cystinosin, a lysosomal cystine–proton symporter[2]. Over 170 pathogenic *CTNS* variants have been identified, including deletion, nonsense and frameshift variants, reflecting significant genotypic diversity across different populations and geographic regions[3]. 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 cases[1]. An intermediate form, termed juvenile or 'late-onset' cystinosis (OMIM 219900) represents 5% of cases[1]. Ocular cystinosis (OMIM 219750) is exceptionally rare and is characterized by isolated corneal cystine crystal deposits without other substantial systemic manifestations[1]. 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 *TRPV1*. 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 cystinosin 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]. Cystinosin can interact with numerous proteins, including components of the vacuolar H^+-ATPase–Ragulator–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 considerably[21]. 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 disorder[30]. 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 Management[31]. 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 guidelines[32], 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-Analyses[33] and Cochrane guidelines. Detailed assessments of the PICO questions related to these CPRs and the corresponding levels of evidence are available elsewhere[34].

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

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 life[35]. Symptoms include polyuria, polydipsia, dehydration, failure to thrive, vomiting, feeding difficulties, growth retardation and signs of rickets[36]. 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 years[27] (Fig. 1). By 2 years of age, cystine crystals can be observed in the cornea, causing progressive photophobia[37].

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 diagnosis[38]. 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-twenties[38].

Ocular cystinosis is extremely rare. Patients accumulate cystine crystals in their cornea, causing photophobia, without overt signs of systemic disease[39]. 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* variants[40], detection of increased leukocyte cystine levels[1] and ophthalmological examination of the anterior segment of the eye (usually by slit-lamp examination) showing cystine crystals in the cornea[37], 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 testing[36].

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 RNA[41] or intronic sequencing. Occasionally, patients with low initial leukocyte cystine levels have been described[42]. In these individuals, fibroblast cultures might be needed to demonstrate increased lysosomal cystine accumulation[42]. After the age of 2 years, all patients with cystinosis have corneal cystine crystal depositions, confirming the diagnosis[37].

Cystine can be measured in mixed leukocyte or pure granulocyte samples[43]. 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 measurements[44]. Lysosome content varies in different leukocyte sub-populations. Granulocytes, which are rich in lysosomes, have a higher cystine content than lymphocytes[45]. Thus, the leukocyte composition influences cystine determination when using mixed leukocyte samples[46]. Measurements require highly standardized protocols that have been developed in specialized laboratories[47]. Leukocyte

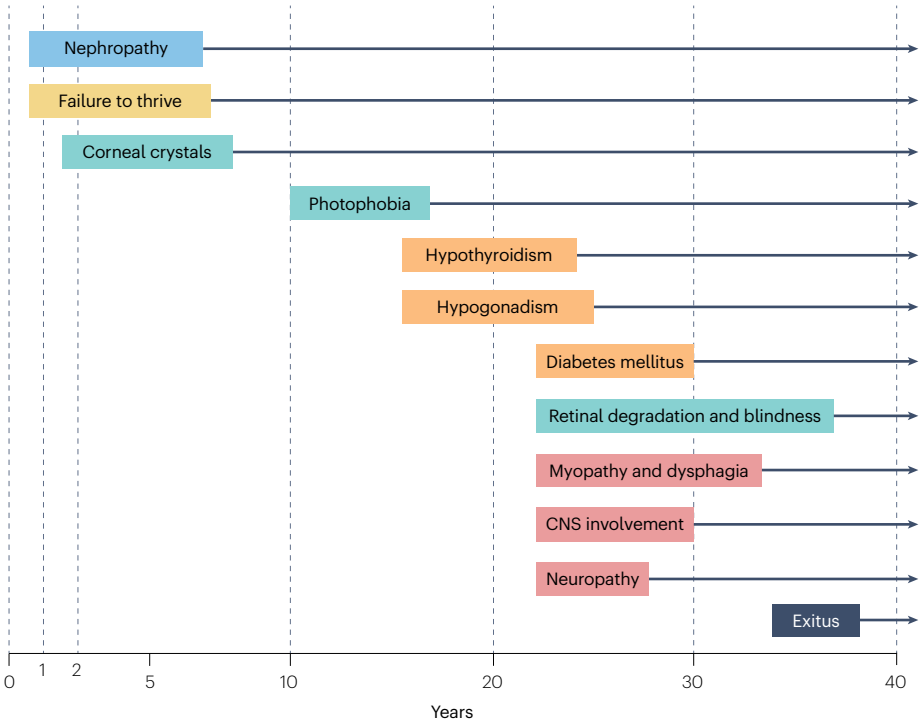

Fig. 1 | Indicative chronology of complications in patients not treated or poorly treated with cysteamine. Patients with infantile nephropathic cystinosis who are not treated with cysteamine typically develop Fanconi syndrome by 1 year of age, at which point and they would also exhibit failure to thrive; 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 treatment[48], 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 years[37].

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 life[26].

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 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 sulfhydryl 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 adulthood[59]. 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/m^2/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 dose[62]. If well tolerated, dosage can be increased more rapidly. An optimized scheme for reaching appropriate cystine depletion using weight-adjusted doses has been reported[63] (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 cysteamine[54] and/or copper deficiency[64].

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/m^2/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 proteinuria[70]. Together with the worsening of tubular lesions, these effects can lead to increased proteinuria over time[71]. 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 syndrome[26].

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 hyphosphataemia[74], Bartter syndrome[75] 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 dialysis[205] (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 progressively[62] (expert-based, strong consensus, additional recommendation)

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)

acidosis[76]) 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).

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 polyuria[87]. 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 transplantation[94] 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 cells[97] (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 status[110]. Most patients have low body mass index (BMI) and reduced muscle mass[111]. They require individualized dietetic management to guarantee optimal nutritional intake.

The Global Leadership Initiative on Malnutrition (GLIM) criteria also apply to adults with cystinosis[112]. All patients should be evaluated following a structured diagnostic scheme[112]. An integrated approach with a team of nephrologists, gastroenterologists, dieticians, 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

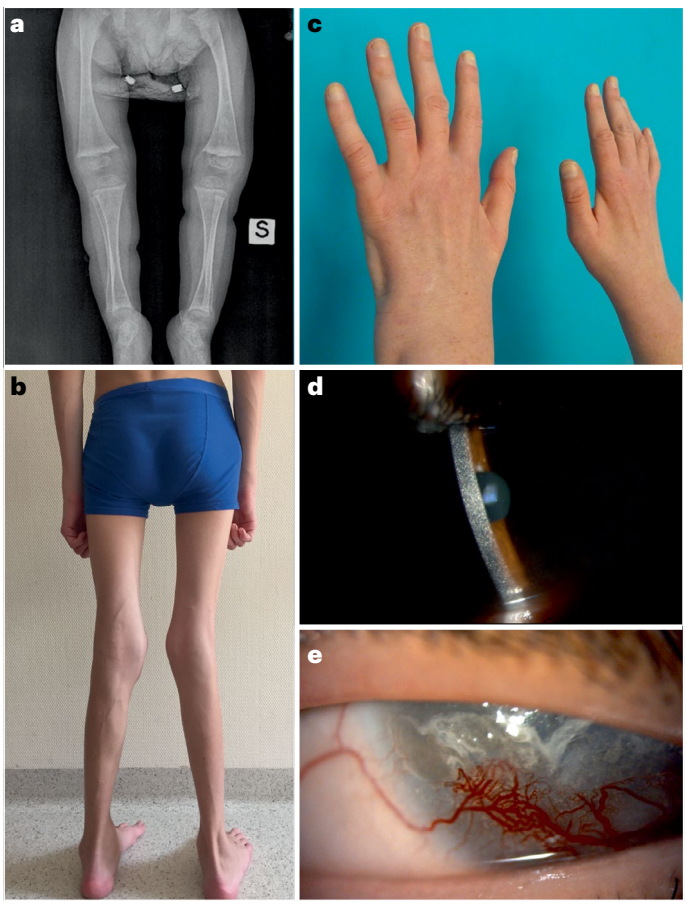

Fig. 2 | Clinical features of patients with infantile nephropathic cystinosis. **a**, X-ray of the lower limbs of an infant with overt rickets secondary to Fanconi syndrome. **b**, Genu valga and limb asymmetry in an adolescent male patient. **c**, Hand muscle wasting in an adult patient with cystinosis-related 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 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 encouraged[113].

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 symptoms[119] 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 standpoint[52]. 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 appropriate[93]. 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 parenchyma[120].

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

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 apparent[123]. 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 gonadic 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[65,208,209]. Dose requirements might be initially higher. Serum 25(OH) vitamin D, Ca, phosphate, ALP and bicarbonate ($HCO3^-$) should be kept within the normal range for age, although $HCO3^-$ 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 recommended[211], 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 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 Disease[212] and the Clinical Practice Recommendations from the Paediatric Renal Nutrition Task force[213] in children with nephropathic cystinosis, as well as the Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in adult patients[212] (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 hypothyroidism[124] (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 population[126]. 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 population[127].

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 steatorrhoea 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 years[28]. Subsequent data indicate reduced incidence and prevalence of diabetes mellitus in people with cystinosis[129]. 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 study[138] 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 malformation[139]. 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)

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

ENT, ear-nose-throat. [a]Dependent on age and method availability. [b]Dependent 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 inclusions[144]. The severity of myopathy correlates with age and disease duration[146] 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 muscles[149]. 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 function[150] (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 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 it[159]. 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 children[160].

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 monitored[162]. 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 population[165] (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.

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 preeclampsia[171]) are the severity of CKD, hypertension and proteinuria[172,173]. Foetuses are also at a higher risk of intrauterine growth retardation, prematurity and death[171].

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 minimal[177]. The child was breastfed for 4 months and had typical growth and development at 18 months of age[177]. 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 diligently[178]. Cystine crystals accumulate in virtually all ocular structures, including the cornea, conjunctiva, iris, lens, optic nerve, retina and choroid[179]. 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 surgery[181].

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 glaucoma[182]. 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 loss[183]. 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 loss[184]. 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)

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 fundoscopy (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 aspects[189], 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,

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 diseases[194]. 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 patients[201] and cost-containment[202]. 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 levels[188] (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)

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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References

1. Gahl, W. A., Thoene, J. G. & Schneider, J. A. Cystinosis. *N. Engl. J. Med.* **347**, 111–121 (2002).
2. Town, M. et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. *Nat. Genet.* **18**, 319–324 (1998).
3. David, D. et al. Molecular basis of cystinosis: geographic distribution, functional consequences of mutations in the CTNS gene, and potential for repair. *Nephron* **141**, 133–146 (2019).
4. Gahl, W. A., Balog, J. Z. & Kleta, R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann. Intern. Med.* **147**, 242–250 (2007).
5. Kalatzis, V., Nevo, N., Cherqui, S., Gasnier, B. & Antignac, C. Molecular pathogenesis of cystinosis: effect of CTNS mutations on the transport activity and subcellular localization of cystinosin. *Hum. Mol. Genet.* **13**, 1361–1371 (2004).
6. Attard, M. et al. Severity of phenotype in cystinosis varies with mutations in the CTNS gene: predicted effect on the model of cystinosin. *Hum. Mol. Genet.* **8**, 2507–2514 (1999).
7. Topaloglu, R. Nephropathic cystinosis: an update on genetic conditioning. *Pediatr. Nephrol.* **36**, 1347–1352 (2021).
8. Anikster, Y., Shotelersuk, V. & Gahl, W. A. CTNS mutations in patients with cystinosis. *Hum. Mutat.* **14**, 454–458 (1999).
9. Shotelersuk, V. et al. CTNS mutations in an American-based population of cystinosis patients. *Am. J. Hum. Genet.* **63**, 1352–1362 (1998).
10. Touchman, J. W. et al. The genomic region encompassing the nephropathic cystinosis gene (CTNS): complete sequencing of a 200-kb segment and discovery of a novel gene within the common cystinosis-causing deletion. *Genome Res.* **10**, 165–173 (2000).
11. Freed, K. A. et al. The 57 kb deletion in cystinosis patients extends into TRPV1 causing dysregulation of transcription in peripheral blood mononuclear cells. *J. Med. Genet.* **48**, 563–566 (2011).
12. Kiehntopf, M. et al. Analysis of the CTNS gene in patients of German and Swiss origin with nephropathic cystinosis. *Hum. Mutat.* **20**, 237–237 (2002).
13. Soliman, N. A. et al. Mutational spectrum of the CTNS gene in Egyptian patients with nephropathic cystinosis. *JIMD Rep.* **14**, 87–97 (2014).
14. Mason, S. et al. Mutational spectrum of the CTNS gene in Italy. *Eur. J. Hum. Genet.* **11**, 503–508 (2003).
15. Cherqui, S. & Courtoy, P. J. The renal Fanconi syndrome in cystinosis: pathogenic insights and therapeutic perspectives. *Nat. Rev. Nephrol.* **13**, 115–131 (2017).
16. Guo, X. et al. Structure and mechanism of human cystine exporter cystinosin. *Cell* **185**, 3739–3752.e18 (2022).
17. Berquez, M. et al. Lysosomal cystine export regulates mTORC1 signaling to guide kidney epithelial cell fate specialization. *Nat. Commun.* **14**, 3994 (2023).
18. Ivanova, E. A. et al. Altered mTOR signalling in nephropathic cystinosis. *J. Inherit. Metab. Dis.* **39**, 457–464 (2016).
19. Rega, L. R. et al. Activation of the transcription factor EB rescues lysosomal abnormalities in cystinotic kidney cells. *Kidney Int.* **89**, 862–873 (2016).
20. Andrzejewska, Z. et al. Cystinosin is a component of the vacuolar H+-ATPase-Ragulator-Rag complex controlling mammalian target of Rapamycin Complex 1 Signaling. *J. Am. Soc. Nephrol.* **27**, 1678–1688 (2016).
21. Thoene, J. G., Oshima, R. G., Crawhall, J. C., Olson, D. L. & Schneider, J. A. Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo. *J. Clin. Invest.* **58**, 180–189 (1976).
22. Pisoni, R. L., Thoene, J. G. & Christensen, H. N. Detection and characterization of carrier-mediated cationic amino acid transport in lysosomes of normal and cystinotic human fibroblasts. Role in therapeutic cystine removal? *J. Biol. Chem.* **260**, 4791–4798 (1985).
23. Jezegou, A. et al. Heptahelical protein PQLC2 is a lysosomal cationic amino acid exporter underlying the action of cysteamine in cystinosis therapy. *Proc. Natl Acad. Sci. USA* **109**, E3434–E3443 (2012).
24. Veys, K. et al. Outcome of infantile nephropathic cystinosis depends on early intervention, not genotype: a multicenter sibling cohort study. *J. Inherit. Metab. Dis.* **46**, 43–54 (2023).
25. Niesl, C. et al. Relationship between age at initiation of cysteamine treatment, adherence with therapy, and glomerular kidney function in infantile nephropathic cystinosis. *Mol. Genet. Meta* **136**, 268–273 (2022).
26. Hohenfellner, K. et al. Beneficial effects of starting oral cysteamine treatment in the first 2 months of life on glomerular and tubular kidney function in infantile nephropathic cystinosis. *Mol. Genet. Metab.* **136**, 282–288 (2022).
27. Markello, T. C., Bernardini, I. M. & Gahl, W. A. Improved renal function in children with cystinosis treated with cysteamine. *N. Engl. J. Med.* **328**, 1157–1162 (1993).
28. Brodin-Sartorius, A. et al. Cysteamine therapy delays the progression of nephropathic cystinosis in late adolescents and adults. *Kidney Int.* **81**, 179–189 (2012).
29. Gahl, W. A. et al. Cysteamine therapy for children with nephropathic cystinosis. *N. Engl. J. Med.* **316**, 971–977 (1987).
30. Golestaneh, L. et al. Improving lifelong comprehensive care coordination in nephropathic cystinosis: multidisciplinary perspectives. *Kidney Int. Rep.* **11**, 103735 (2026).
31. Nothacker, M. et al. AWMF Guidance Manual and Rules for Guideline Development. https://www.awmf.org/fileadmin/user_upload/dateien/downloads_regelwerk/awmf-regelwerk-en-2023-v2.1.pdf (2023).
32. Butcher, N. J. et al. Guidelines for reporting outcomes in trial reports. *JAMA* **328**, 2252–2264 (2022).
33. Page, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021).
34. Ledinger, D. et al. Diagnosis and management of cystinosis: systematic review for a clinical practice guideline. *Orphanet J. Rare Dis.* **20**, 463 (2025).
35. Emma, F. et al. An international cohort study spanning five decades assessed outcomes of nephropathic cystinosis. *Kidney Int.* **100**, 1112–1123 (2021).
36. Gahl, W. A. & Nesterova, N. Cystinosis. *Gene Reviews*. https://www.ncbi.nlm.nih.gov/books/NBK1400/. Accessed 14 August 2025.
37. Gahl, W. A., Kuehl, E. M., Iwata, F., Lindblad, A. & Kaiser-Kupfer, M. I. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. *Mol. Genet. Metab.* **71**, 100–120 (2000).
38. Servais, A. et al. Late-onset nephropathic cystinosis: clinical presentation, outcome, and genotyping. *Clin. J. Am. Soc. Nephrol.* **3**, 27–35 (2008).
39. Anikster, Y. et al. Ocular nonnephropathic cystinosis: clinical, biochemical, and molecular correlations. *Pediatr. Res.* **47**, 17–23 (2000).
40. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **17**, 405–423 (2015).
41. Taranta, A. et al. Analysis of CTNS gene transcripts in nephropathic cystinosis. *Pediatr. Nephrol.* **25**, 1263–1267 (2010).
42. Bondue, T. et al. The pitfall of white blood cell cystine measurement to diagnose juvenile cystinosis. *Int. J. Mol. Sci.* **24**, 1253 (2023).
43. Gahl, W. A., Thoene, J. G., Schneider, J. A. Scriver, C. R., Beaudet, A. L., Sly, W. S., Valle, D. (eds). *The Metabolic & Molecular Bases of Inherited Disease*. (McGraw-Hill, 2001)). 5085–5108.
44. Gertsman, I. et al. Diagnosis and monitoring of cystinosis using immunomagnetically purified granulocytes. *Clin. Chem.* **62**, 766–772 (2016).
45. Schulman, J. D., Wong, V. G., Kuwabara, T., Bradley, K. H. & Seegmiller, J. E. Intracellular cystine content of leukocyte populations in cystinosis. *Arch. Intern. Med.* **125**, 660–664 (1970).
46. Smolin, L. A., Clark, K. F. & Schneider, J. A. An improved method for heterozygote detection of cystinosis, using polymorphonuclear leukocytes. *Am. J. Hum. Genet.* **41**, 266–275 (1987).
47. Levtchenko, E. et al. Comparison of cystine determination in mixed leukocytes vs polymorphonuclear leukocytes for diagnosis of cystinosis and monitoring of cysteamine therapy. *Clin. Chem.* **50**, 1686–1688 (2004).
48. Linden, S. et al. Cystinosis: therapy adherence and metabolic monitoring in patients treated with immediate-release cysteamine. *Mol. Genet. Metab. Rep.* **24**, 100620 (2020).
49. Fleige, T. et al. Next generation sequencing as second-tier test in high-throughput newborn screening for nephropathic cystinosis. *Eur. J. Hum. Genet.* **28**, 193–201 (2020).
50. Hohenfellner, K. et al. Molecular based newborn screening in Germany: follow-up for cystinosis. *Mol. Genet. Metab. Rep.* **21**, 100514 (2019).
51. Ahlenstiel-Grunow, T. et al. Switching from immediate- to extended-release cysteamine in nephropathic cystinosis patients: a retrospective real-life single-center study. *Pediatr. Nephrol.* **32**, 91–97 (2017).
52. Langman, C. B. et al. A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. *Clin. J. Am. Soc. Nephrol.* **7**, 1112–1120 (2012).
53. Kleta, R. & Gahl, W. A. Pharmacological treatment of nephropathic cystinosis with cysteamine. *Expert. Opin. Pharmacother.* **5**, 2255–2262 (2004).
54. Besouw, M. T. et al. Cysteamine toxicity in patients with cystinosis. *J. Pediatr.* **159**, 1004–1011 (2011).
55. Besouw, M., Tangerman, A., Cornelissen, E., Rioux, P. & Levtchenko, E. Halitosis in cystinosis patients after administration of immediate-release cysteamine bitartrate compared to delayed-release cysteamine bitartrate. *Mol. Genet. Metab.* **107**, 234–236 (2012).
56. Schneider, J. A. Treatment of cystinosis: simple in principle, difficult in practice. *J. Pediatr.* **145**, 436–438 (2004).
57. Armas, D. et al. A phase 1 pharmacokinetic study of cysteamine bitartrate delayed-release capsules following oral administration with orange juice, water, or omeprazole in cystinosis. *Adv. Ther.* **35**, 199–209 (2018).
58. Ariceta, G., Giordano, V. & Santos, F. Effects of long-term cysteamine treatment in patients with cystinosis. *Pediatr. Nephrol.* **34**, 571–578 (2019).
59. Ariceta, G. et al. Cysteamine (Cystagon®) adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults. *Nephrol. Dial. Transplant.* **30**, 475–480 (2015).
60. Stein, C. et al. A comparison of immediate release and delayed release cysteamine in 17 patients with nephropathic cystinosis. *Orphanet J. Rare Dis.* **16**, 387 (2021).
61. Gaillard, S. et al. Adherence to cysteamine in nephropathic cystinosis: a unique electronic monitoring experience for a better understanding. A prospective cohort study: CrYSTobs. *Pediatr. Nephrol.* **36**, 581–589 (2021).
62. Corden, B. J., Schulman, J. D., Schneider, J. A. & Thoene, J. G. Adverse reactions to oral cysteamine use in nephropathie cystinosis. *Dev. Pharmacol. Ther.* **3**, 25–30 (1981).

63. Bouazza, N. et al. Population pharmacokinetics and pharmacodynamics of cysteamine in nephropathic cystinosis patients. *Orphanet J. Rare Dis.* **6**, 86 (2011).
64. Besouw, M. T. et al. Copper deficiency in patients with cystinosis with cysteamine toxicity. *J. Pediatr.* **163**, 754–760 (2013).
65. Stevens, P. E. et al. KDIGO 2024 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* **105**, S117–S314 (2024).
66. Shroff, R. et al. Vascular access in children requiring maintenance haemodialysis: a consensus document by the European Society for Paediatric Nephrology Dialysis Working Group. *Nephrol. Dial. Transplant.* **34**, 1746–1765 (2019).
67. Mahoney, C. P. & Striker, G. E. Early development of the renal lesions in infantile cystinosis. *Pediatr. Nephrol.* **15**, 50–56 (2000).
68. Langman, C. B. et al. Controversies and research agenda in nephropathic cystinosis: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int.* **89**, 1192–1203 (2016).
69. Foreman, J. W. Fanconi Syndrome. *Pediatr. Clinic. North. Am.* **66**, 159–167 (2019).
70. Wilmer, M. J., Christensen, E. I., Heuvel, L. P., van den, Monnens, L. A. & Levtchenko, E. N. Urinary protein excretion pattern and renal expression of megalin and cubilin in nephropathic cystinosis. *Am. J. Kidney Dis.* **51**, 893–903 (2008).
71. Ivanova, E. A. et al. Cystinosin deficiency causes podocyte damage and loss associated with increased cell motility. *Kidney Int.* **89**, 1037–1048 (2016).
72. Kleta, R. et al. Long-term follow-up of well-treated nephropathic cystinosis patients. *J. Pediatr.* **145**, 555–560 (2004).
73. Nesterova, G., Williams, C., Bernardini, I. & Gahl, W. A. Cystinosis: renal glomerular and renal tubular function in relation to compliance with cystine-depleting therapy. *Pediatr. Nephrol.* **30**, 945–951 (2015).
74. Haffner, D. et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat. Rev. Nephrol.* **21**, 330–354 (2025).
75. Konrad, M. et al. Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders. *Kidney Int* **99**, 324–335 (2021).
76. Trepiccione, F. et al. Distal renal tubular acidosis: ERKNet/ESPN clinical practice points. *Nephrol. Dial. Transplant.* **36**, 1585–1596 (2021).
77. Callis, L., Castello, F., Fortuny, G., Vallo, A. & Ballabriga, A. Effect of hydrochlorothiazide on rickets and on renal tubular acidosis in two patients with cystinosis. *Helv. Paediatr. Acta* **25**, 602–619 (1970).
78. Calò, S. & Console, V. [Effect of hydrochlorothiazide on proximal tubular acidosis calciuria and phosphaturia in a case of cystinosis]. *Minerva Pediatr.* **23**, 461–466 (1971).
79. Senecky, Y., Lison, M., Katznelson, D., Orda, S. & Aladjem, M. Treatment of proximal renal tubular acidosis with a thiazide diuretic]. *Harefuah* **104**, 14–16 (1983).
80. Betend, B., David, L., Vincent, M., Hermier, M. & Francois, R. Successful indomethacin treatment of two paediatric patients with severe tubulopathies. A boy with an unusual hypercalciuria and a girl with cystinosis. *Helv. Paediatr. Acta* **34**, 339–344 (1979).
81. Haycock, G. B., Al-Dahhan, J., Mak, R. H. & Chantler, C. Effect of indomethacin on clinical progress and renal function in cystinosis. *Arch. Dis. Child.* **57**, 934 (1982).
82. Greco, M. et al. Long-term outcome of nephropathic cystinosis: a 20-year single-center experience. *Pediatr. Nephrol.* **25**, 2459–2467 (2010).
83. Wühl, E. et al. Strict blood-pressure control and progression of renal failure in children. *N. Engl. J. Med.* **361**, 1639–1650 (2009).
84. Ruggenenti, P. et al. Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. The "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int. Suppl.* **63**, S54–S57 (1997).
85. Flynn, J. T. et al. Clinical Practice Guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* **140**, e20171904 (2017).
86. Cheung, A. K. et al. KDIGO 2021 Clinical Practice Guideline for the management of blood pressure in chronic kidney disease. *Kidney Int.* **99**, S1–S87 (2021).
87. Sharbaf, F. G. et al. Native nephrectomy prior to pediatric kidney transplantation: biological and clinical aspects. *Pediatr. Nephrol.* **27**, 1179–1188 (2012).
88. Cohen, C. et al. Excellent long-term outcome of renal transplantation in cystinosis patients. *Orphanet J. Rare Dis.* **10**, 90 (2015).
89. Kizilbash, S. J., Snyder, J., Vock, D. M. & Chavers, B. M. Trends in kidney transplant outcomes in children and young adults with cystinosis. *Pediatr. Transplant.* **23**, e13572 (2019).
90. Stralen, K. J. et al. Improvement in the renal prognosis in nephropathic cystinosis. *Clin. J. Am. Soc. Nephrol.* **6**, 2485–2491 (2011).
91. Kashtan, C. E., McEnery, P. T., Tejani, A. & Stablein, D. M. Renal allograft survival according to primary diagnosis: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr. Nephrol.* **9**, 679–684 (1995).
92. Spicer, R. A., Clayton, P. A., McTaggart, S. J., Zhang, G. Y. & Alexander, S. I. Patient and graft survival following kidney transplantation in recipients with cystinosis: a cohort study. *Am. J. Kidney Dis.* **65**, 172–173 (2015).
93. Chang, H. E. et al. Long-term outcomes in nephropathic cystinosis: a review. *Pediatr. Nephrol.* **41**, 277–296, https://doi.org/10.1007/s00467-025-06790-6 (2026).
94. Berryhill, A., Bhamre, S., Chaudhuri, A., Concepcion, W. & Grimm, P. C. Cysteamine in renal transplantation: a report of two patients with nephropathic cystinosis and the successful re-initiation of cysteamine therapy during the immediate post-transplant period. *Pediatr. Transplant.* **20**, 141–145 (2016).
95. Hohenfellner, K. et al. Management of bone disease in cystinosis: statement from an international conference. *J. Inherit. Metab. Dis.* **42**, 1019–1029 (2019).
96. Bertholet-Thomas, A. et al. Teenagers and young adults with nephropathic cystinosis display significant bone disease and cortical impairment. *Pediatr. Nephrol.* **33**, 1165–1172 (2018).
97. Haffner, D., Leifheit-Nestler, M., Alioli, C. & Bacchetta, J. Muscle and bone impairment in infantile nephropathic cystinosis: new concepts. *Cells* **11**, 05 (2022).
98. Florenzano, P. et al. Skeletal consequences of nephropathic cystinosis. *J. Bone Miner. Res.* **33**, 1870–1880 (2018).
99. Ewert, A. et al. Bone and mineral metabolism in children with nephropathic cystinosis compared with other CKD entities. *J. Clin. Endocrinol. Metab.* **105**, 01 (2020).
100. Bacchetta, J. et al. Skeletal implications and management of cystinosis: three case reports and literature review. *Bonekey Rep.* **5**, 828 (2016).
101. Pozza, S. B.-D. et al. Cortical impairment and reduced muscle mass in children and young adults with nephropathic cystinosis. *J. Bone Miner. Res.* **39**, 1094–1102 (2024).
102. Lahring, J. et al. Cystinosis-associated metabolic bone disease across ages and CKD stages 1 to 5D/T. *J. Clin. Endocrinol. Metab.* **110**, e218–e230 (2025).
103. Battafarano, G. et al. Intrinsic bone defects in cystinotic mice. *Am. J. Pathol.* **189**, 1053–1064 (2019).
104. Claramunt-Taberner, D. et al. Bone disease in nephropathic cystinosis is related to cystinosin-induced osteoclastic dysfunction. *Nephrol. Dial. Transplant.* **33**, 1525–1532 (2018).
105. Florenzano, P. et al. Nephropathic cystinosis: a distinct form of CKD-mineral and bone disorder that provides novel insights into the regulation of FGF23. *J. Am. Soc. Nephrol.* **31**, 2184–2192 (2020).
106. Elenberg, E., Norling, L. L., Kleinman, R. E. & Ingelfinger, J. R. Feeding problems in cystinosis. *Pediatr. Nephrol.* **12**, 365–370 (1998).
107. Nakhaii, S., Hooman, N. & Otukesh, H. Gastrointestinal manifestations of nephropathic cystinosis in children. *Iran. J. Kidney Dis.* **3**, 218–221 (2009).
108. Nakhaie, S. et al. Gastrointestinal manifestations of adult cystinosis in Iran: a descriptive study. *Med. J. Islam. Repub. Iran* **36**, 15 (2022).
109. Joseph, M. W., Stein, D. R. & Stein, A. C. Gastrointestinal challenges in nephropathic cystinosis: clinical perspectives. *Pediatr. Nephrol.* **39**, 2845–2860 (2024).
110. Iorember, F. M. Malnutrition in chronic kidney disease. *Front. Pediatr.* **6**, 161 (2018).
111. Rashid, R. et al. Body composition and nutritional intake in children with chronic kidney disease. *Pediatr. Nephrol.* **21**, 1730–1738 (2006).
112. Jensen, G. L. et al. GLIM consensus approach to diagnosis of malnutrition: a 5-year update. *J. Parenter. Enter. Nutr.* **49**, 414–427 (2025).
113. Mahboobi, S. et al. Effects of dietary interventions for metabolic acidosis in chronic kidney disease: a systematic review and meta-analysis. *Nephrol. Dial. Transplant.* **40**, 751–767 (2024).
114. Homan, M. et al. Percutaneous endoscopic gastrostomy in children: an update to the ESPGHAN position paper. *J. Pediatr. Gastroenterol. Nutr.* **73**, 415–426 (2021).
115. Kohli, D. R. et al. American Society for Gastrointestinal Endoscopy guideline on gastrostomy feeding tubes: summary and recommendations. *Gastrointest. Endosc.* **101**, 25–35 (2025).
116. Rees, L. et al. Delivery of a nutritional prescription by enteral tube feeding in children with chronic kidney disease stages 2–5 and on dialysis — clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr. Nephrol.* **36**, 187–204 (2021).
117. Rijssel, A. E. van, Knuijt, S., Veys, K., Levtchenko, E. N. & Janssen, M. C. H. Swallowing dysfunction in patients with nephropathic cystinosis. *Mol. Genet. Metab.* **126**, 413–415 (2019).
118. Wenner, W. J. & Murphy, J. L. The effects of cysteamine on the upper gastrointestinal tract of children with cystinosis. *Pediatr. Nephrol.* **11**, 600–603 (1997).
119. Dohil, R. et al. Esomeprazole therapy for gastric acid hypersecretion in children with cystinosis. *Pediatr. Nephrol.* **20**, 1786–1793 (2005).
120. Chevronnay, H. P. G. et al. A mouse model suggests two mechanisms for thyroid alterations in infantile cystinosis: decreased thyroglobulin synthesis due to endoplasmic reticulum stress/unfolded protein response and impaired lysosomal processing. *Endocrinology* **156**, 2349–2364 (2015).
121. Veys, K. R., Elmonem, M. A., Arcolino, F. O., Heuvel, L. vanden & Levtchenko, E. Nephropathic cystinosis: an update. *Curr. Opin. Pediatr.* **29**, 168–178 (2017).
122. Kimonis, V. E. et al. Effects of early cysteamine therapy on thyroid function and growth in nephropathic cystinosis. *J. Clin. Endocrinol. Metab.* **80**, 3257–3261 (1995).
123. Bako, D., Kılavuz, S., Köksoy, A. Y., Tatli, Z. U. & Beydogan, E. A different approach to cystinosis: ultrasound, Doppler, and shear wave elastography findings of thyroid gland. *Orphanet J. Rare Dis.* **18**, 173 (2023).
124. Jonklaas, J. et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid* **24**, 1670–1751 (2014).
125. Filler, G., Amendt, P., Bredow, M. A., Rohde, W. & Ehrich, J. H. Slowly deteriorating insulin secretion and C-peptide production characterizes diabetes mellitus in infantile cystinosis. *Eur. J. Pediatr.* **157**, 738–742 (1998).
126. ElSayed, N. A. et al. 2. Diagnosis and classification of diabetes: standards of care in diabetes — 2024. *Diabetes Care* **47**, S20–S42 (2023).
127. ElSayed, N. A. et al. 3. Prevention or delay of diabetes and associated comorbidities: standards of care in diabetes — 2024. *Diabetes Care* **47**, S43–S51 (2023).
128. Robert, J. J. et al. Diabetes mellitus in patients with infantile cystinosis after renal transplantation. *Pediatr. Nephrol.* **13**, 524–529 (1999).
129. Servais, A. et al. #4432 ECYSCO: a European cohort dedicated to cystinosis. *Nephrol. Dial. Transplant.* **38**, gfad063a_4432 (2023).
130. Prokai, A. et al. The importance of different immunosuppressive regimens in the development of posttransplant diabetes mellitus. *Pediatr. Diabetes* **13**, 81–91 (2012).

131. Prokai, A. et al. Post-transplant diabetes mellitus in children following renal transplantation. *Pediatr. Transplant.* **12**, 643–649 (2008).
132. Trauner, D. Neurocognitive complications of cystinosis. *J. Pediatr.* **183S**, S15–S18 (2017).
133. Trauner, D. A., Spilkin, A. M., Williams, J. & Babchuck, L. Specific cognitive deficits in young children with cystinosis: evidence for an early effect of the cystinosin gene on neural function. *J. Pediatr.* **151**, 192–196 (2007).
134. Scarvie, K. M., Ballantyne, A. O. & Trauner, D. A. Visuomotor performance in children with infantile nephropathic cystinosis. *Percept. Mot. Skills* **82**, 67–75 (1996).
135. Spilkin, A. M., Ballantyne, A. O., Babchuck, L. R. & Trauner, D. A. Non-verbal deficits in young children with a genetic metabolic disorder: WPPSI-III performance in cystinosis. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **144B**, 444–447 (2007).
136. Besouw, M. T. et al. Neurocognitive functioning in school-aged cystinosis patients. *J. Inherit. Metab. Dis.* **33**, 787–793 (2010).
137. Burgac, E. et al. Neurological involvement in 51 cystinosis patients: a single-center experience. *Eur. J. Paediatr. Neurol.* **57**, 50–56 (2025).
138. Spilkin, A. M., Ballantyne, A. O. & Trauner, D. A. Visual and verbal learning in a genetic metabolic disorder. *Neuropsychologia* **47**, 1883–1892 (2009).
139. Rao, K. I., Hesselink, J. & Trauner, D. A. Chiari I malformation in nephropathic cystinosis. *J. Pediatr.* **167**, 1126–1129 (2015).
140. Bava, S. et al. Developmental changes in cerebral white matter microstructure in a disorder of lysosomal storage. *Cortex* **46**, 206–216 (2010).
141. Curie, A. et al. Neuropsychological and neuroanatomical phenotype in 17 patients with cystinosis. *Orphanet J. Rare Dis.* **15**, 59 (2020).
142. Servais, A. et al. Central nervous system complications in adult cystinosis patients. *J. Inherit. Metab. Dis.* **43**, 348–356 (2020).
143. Gahl, W. A. et al. Myopathy and cystine storage in muscles in a patient with nephropathic cystinosis. *N. Engl. J. Med.* **319**, 1461–1464 (1988).
144. Charnas, L. R. et al. Distal vacuolar myopathy in nephropathic cystinosis. *Ann. Neurol.* **35**, 181–188 (1994).
145. Cabrera-Serrano, M. et al. Cystinosis distal myopathy, novel clinical, pathological and genetic features. *Neuromuscul. Disord.* **27**, 873–878 (2017).
146. Vill, K. et al. Neuromuscular conditions and the impact of cystine-depleting therapy in infantile nephropathic cystinosis: a cross-sectional analysis of 55 patients. *J. Inherit. Metab. Dis.* **45**, 183–191 (2022).
147. Elkhateeb, N. et al. Clinical and neurophysiological characterization of early neuromuscular involvement in children and adolescents with nephropathic cystinosis. *Pediatr. Nephrol.* **37**, 1555–1566 (2022).
148. Sadjadi, R. et al. Clinical myopathy in patients with nephropathic cystinosis. *Muscle Nerve* **61**, 74–80 (2020).
149. Anikster, Y. et al. Pulmonary dysfunction in adults with nephropathic cystinosis. *Chest* **119**, 394–401 (2001).
150. Sadjadi, R. et al. Clinical trial readiness study of distal myopathy and dysphagia in nephropathic cystinosis. *Muscle Nerve* **62**, 681–687 (2020).
151. Bernardini, I., Rizzo, W. B., Dalakas, M., Bernar, J. & Gahl, W. A. Plasma and muscle free carnitine deficiency due to renal Fanconi syndrome. *J. Clin. Invest.* **75**, 1124–1130 (1985).
152. Gahl, W. A. et al. Oral carnitine therapy in children with cystinosis and renal Fanconi syndrome. *J. Clin. Invest.* **81**, 549–560 (1988).
153. Gahl, W. A. et al. Muscle carnitine repletion by long-term carnitine supplementation in nephropathic cystinosis. *Pediatr. Res.* **34**, 115–119 (1993).
154. Calatayud, M. T. et al. [Treatment with ubiquinone in Kearns-Sayre syndrome. Improvement in ocular motility and visual evoked potentials]. *Neurologia* **7**, 266–269 (1992).
155. Ambrose, A. et al. Outcomes of mitochondrial long chain fatty acid oxidation and carnitine defects from a single center metabolic genetics clinic. *Orphanet J. Rare Dis.* **17**, 360 (2022).
156. Abrahamsen, R. K., Lund, A. M. & Rasmussen, J. Patients with primary carnitine deficiency treated with L-carnitine are alive and doing well — a 10-year follow-up in the Faroe Islands. *JIMD Rep.* **64**, 453–459 (2023).
157. Rohayem, J. et al. Testicular function in males with infantile nephropathic cystinosis. *Hum. Reprod.* **36**, 1191–1204 (2021).
158. Reda, A., Veys, K. & Besouw, M. Fertility in cystinosis. *Cells* **10**, 15 (2021).
159. Besouw, M. T., Kremer, J. A., Janssen, M. C. & Levtchenko, E. N. Fertility status in male cystinosis patients treated with cysteamine. *Fertil. Steril.* **93**, 1880–1883 (2010).
160. Veys, K. R. et al. First successful conception induced by a male cystinosis patient. *JIMD Rep.* **38**, 1–6 (2018).
161. Chik, C. L., Friedman, A., Merriam, G. R. & Gahl, W. A. Pituitary-testicular function in nephropathic cystinosis. *Ann. Intern. Med.* **119**, 568–575 (1993).
162. Snyder, P. J. et al. Lessons from the testosterone trials. *Endocr. Rev.* **39**, 369–386 (2018).
163. Salonia, A. et al. European Association of Urology guidelines on sexual and reproductive health — 2021 update: male sexual dysfunction. *Eur. Urol.* **80**, 333–357 (2021).
164. Corona, G. et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization: European Society of Endocrinology. *Andrology* **8**, 970–987 (2020).
165. Saad, F. et al. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur. J. Endocrinol.* **165**, 675–685 (2011).
166. Blakey, H., Proudfoot-Jones, J., Knox, E. & Lipkin, G. Pregnancy in women with cystinosis. *Clin. Kidney J.* **12**, 855–858 (2019).
167. Haase, M. et al. Successful pregnancies in dialysis patients including those suffering from cystinosis and familial Mediterranean fever. *J. Nephrol.* **19**, 677–681 (2006).
168. Andrews, P. A., Sacks, S. H. & Hoff, W. V. Successful pregnancy in cystinosis. *JAMA* **272**, 1327–1328 (1994).
169. Servais, A. et al. Pregnancy in cystinosis patients with chronic kidney disease: a European case series. *J. Inherit. Metab. Dis.* **45**, 963–968 (2022).
170. Robertson, G. et al. A successful adolescent pregnancy in a patient with cystinosis and CKD not yet on kidney replacement therapy. *Kidney Int. Rep.* **7**, 1711–1715 (2022).
171. Langman, C. B. et al. Fertility management in cystinosis: a clinical perspective. *Kidney Int. Rep.* **9**, 214–224 (2024).
172. Piccoli, G. B. et al. Risk of adverse pregnancy outcomes in women with CKD. *J. Am. Soc. Nephrol.* **26**, 2011–2022 (2015).
173. Bramham, K. et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin. J. Am. Soc. Nephrol.* **8**, 290–298 (2013).
174. Reiss, R. E., Kuwabara, T., Smith, M. L. & Gahl, W. A. Successful pregnancy despite placental cystine crystals in a woman with nephropathic cystinosis. *N. Engl. J. Med.* **319**, 223–226 (1988).
175. Kuczborska, K. et al. Therapeutic problems and pregnancy in a patient with infantile nephropathic cystinosis: a case report. *Transplant. Proc.* **51**, 545–547 (2019).
176. McKay, D. B. & Josephson, M. A. Pregnancy after kidney transplantation. *Clin. J. Am. Soc. Nephrol.* **3**, S117–S125 (2008).
177. Chan, L. et al. Pregnancy and breastfeeding in nephropathic cystinosis with native kidneys. *Kidney Int. Rep.* **7**, 1716–1719 (2022).
178. Bishop, R. Ocular complications of infantile nephropathic cystinosis. *J. Pediatr.* **183S**, S19–S21 (2017).
179. Tsilou, E., Zhou, M., Gahl, W., Sieving, P. C. & Chan, C.-C. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature. *Surv. Ophthalmol.* **52**, 97–105 (2007).
180. Kaiser-Kupfer, M. I., Fujikawa, L., Kuwabara, T., Jain, S. & Gahl, W. A. Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. *N. Engl. J. Med.* **316**, 775–779 (1987).
181. Kaiser-Kupfer, M. I., Datiles, M. B. & Gahl, W. A. Corneal transplant in boy with nephropathic cystinosis. *Lancet* **1**, 331 (1987).
182. Wan, W. L., Minckler, D. S. & Rao, N. A. Pupillary-block glaucoma associated with childhood cystinosis. *Am. J. Ophthalmol.* **101**, 700–705 (1986).
183. Tsilou, E. T. et al. Nephropathic cystinosis: posterior segment manifestations and effects of cysteamine therapy. *Ophthalmology* **113**, 1002–1009 (2006).
184. Dogulu, C. F. et al. Idiopathic intracranial hypertension in cystinosis. *J. Pediatr.* **145**, 673–678 (2004).
185. Ghosh, S., O'Hare, F., Lamoureux, E., Vajpayee, R. B. & Crowston, J. G. Prevalence of signs and symptoms of ocular surface disease in individuals treated and not treated with glaucoma medication. *Clin. Exp. Ophthalmol.* **40**, 675–681 (2012).
186. Valente, C., Iester, M., Corsi, E. & Rolando, M. Symptoms and signs of tear film dysfunction in glaucomatous patients. *J. Ocul. Pharmacol. Ther.* **27**, 281–285 (2011).
187. Beinart, N., Hackett, R. A., Graham, C. D., Weinman, J. & Ostermann, M. Mood and illness experiences of adults with cystinosis. *Ren. Fail.* **37**, 835–839 (2015).
188. Witt, S., Kristensen, K., Hohenfellner, K. & Quitmann, J. Health-related quality of life and patient-reported outcome measurements in patients with cystinosis. *JIMD. Rep.* **64**, 199–211 (2023).
189. Witt, S., Schuett, K., Wiegand-Grefe, S., Boettcher, J. & Quitmann, J. Living with a rare disease - experiences and needs in pediatric patients and their parents. *Orphanet J. Rare Dis.* **18**, 242 (2023).
190. Watson, A. R. Non-compliance and transfer from paediatric to adult transplant unit. *Pediatr. Nephrol.* **14**, 469–472 (2000).
191. Dobbels, F. et al. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr. Transplant.* **14**, 603–613 (2010).
192. Cecka, J. M., Gjertson, D. W. & Terasaki, P. I. Pediatric renal transplantation: a review of the UNOS data. United Network for Organ Sharing. *Pediatr. Transplant.* **1**, 55–64 (1997).
193. Samuel, S. M. et al. Graft failure and adaptation period to adult healthcare centers in pediatric renal transplant patients. *Transplantation* **91**, 1380–1385 (2011).
194. Pape, L. & Ernst, G. Health care transition from pediatric to adult care: an evidence-based guideline. *Eur. J. Pediatr.* **181**, 1951–1958 (2022).
195. Becker, J., Ravens, E., Pape, L. & Ernst, G. Somatic outcomes of young people with chronic diseases participating in transition programs: a systematic review. *J. Transit. Med.* **2**, 20200003 (2020).
196. Crowley, R., Wolfe, I., Lock, K. & McKee, M. Improving the transition between paediatric and adult healthcare: a systematic review. *Arch. Dis. Child.* **96**, 548–553 (2011).
197. Campbell, Z. C. et al. Interventions for improving health literacy in people with chronic kidney disease. *Cochrane Database Syst. Rev.* **2022**, CD012026 (2022).
198. Doyle, M. & Werner-Lin, A. That eagle covering me: transitioning and connected autonomy for emerging adults with cystinosis. *Pediatr. Nephrol.* **30**, 281–291 (2015).
199. Raina, R., Wang, J. & Krishnappa, V. Structured transition protocol for children with cystinosis. *Front. Pediatr.* **5**, 191 (2017).
200. World Health Organization & Cash-Gibson, L. Integrating health services. WHO/HIS/SDS/2018.50 (World Health Organization, 2018).
201. Santis, M. D. & Castro, R. Policy Brief "Integrated Care" 2018. https://www.rd-action.eu/wp-content/uploads/2018/09/INTEGRATED-CARE.pdf (2018).
202. Rocks, S. et al. Cost and effects of integrated care: a systematic literature review and meta-analysis. *Eur. J. Heal. Econ.* **21**, 1211–1221 (2020).
203. Hohenfellner, K. & Deerberg-Wittram, J. Coordinated, cost-effective care for rare disease: The Cystinosis Outpatient Consultation Program at RoMed. *NEJM Catal. Innov. Care Deliv.* **1**, 1 (2020).

204. Ariceta, G. et al. Cystinosis in adult and adolescent patients: recommendations for the comprehensive care of cystinosis. *Nefrologia* **35**, 304–321 (2015).
205. Besouw, M. & Levtchenko, E. Pharmacokinetics of cysteamine in a cystinosis patient treated with hemodialysis. *Pediatr. Nephrol.* **26**, 639–640 (2011).
206. Bakkaloglu, S. A. et al. Bone evaluation in paediatric chronic kidney disease: clinical practice points from the European Society for Paediatric Nephrology CKD-MBD and Dialysis working groups and CKD-MBD working group of the ERA-EDTA. *Nephrol. Dial. Transplant.* **36**, 413–425 (2020).
207. Bacchetta, J. et al. Diagnosis and management of mineral and bone disorders in infants with CKD: clinical practice points from the ESPN CKD-MBD and Dialysis working groups and the Pediatric Renal Nutrition Taskforce. *Pediatr. Nephrol.* **38**, 3163–3181 (2023).
208. Munns, C. F. et al. Global consensus recommendations on prevention and management of nutritional rickets. *J. Clin. Endocrinol. Metab.* **101**, 394–415 (2016).
209. Shroff, R. et al. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease stages 2–5 and on dialysis. *Nephrol. Dial. Transplant.* **32**, 1098–1113 (2017).
210. Jørgensen, H. S. et al. The role of nutritional vitamin D in chronic kidney disease–mineral and bone disorder in children and adults with chronic kidney disease, on dialysis, and after kidney transplantation — a European consensus statement. *Nephrol. Dial. Transpl.* **40**, 797–822 (2025).
211. Drube, J. et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat. Rev. Nephrol.* **15**, 577–589 (2019).
212. Ikizler, T. A. et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 Update. *Am. J. Kidney Dis.* **76**, S1–S107 (2020).
213. Nelms, C. L. et al. Assessment of nutritional status in children with kidney diseases — clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. *Pediatr. Nephrol.* **36**, 995–1010 (2021).

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