

Supplementary information

Clinical practice recommendations for the diagnosis and management of nephropathic cystinosis

**In the format provided by
the authors and unedited**

Supplementary Table 1. Diagnostic tests for cystinosis

Age	Molecular testing	Leukocyte cystine levels	Corneal cystine crystals
Prenatal	Yes	No	No
Neonates	Yes	Yes	No
< 2 years	Yes	Yes	Not always present
≥ 2 years	Yes	Yes	Yes

Supplementary Box 1

Patient version of the cystinosis clinical practice guidelines

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Introduction

This is the patient version of the clinical practice guidelines for the management of nephropathic cystinosis, a rare genetic disorder characterized by the abnormal accumulation of cystine within cells, leading to tissue and organ damage, particularly in the kidneys and eyes. The authors of the medical guidelines are members of relevant medical groups.

All recommendations within the medical guidelines consider the strength of currently available evidence (scientific proof of efficacy or effectiveness, all known associated risks, and patients' acceptance of these risks) and the agreement (consensus) between physicians, psychologists, clinical experts from the fields of physiotherapy, speech therapy, nutritional science, and pharmacology, along with patient representatives. All opinions were collected and considered at a series of consensus conferences, with recommendations which were collectively agreed upon then being adopted.

The patient guidelines adopt the exact recommendations of the clinical guidelines and explains the recommendations in non-scientific, easy-to-follow layman's terms. Without lessening the impact of the guidelines, practical recommendations are also provided based on patient perspectives. For this reason, brochures and information materials provided by patient organisations were also used as reference sources for the patient guidelines. In addition, recommendations were obtained from patients in a multi-step consultation process.

The patient guidelines are intended to help those individuals affected by nephropathic cystinosis and their relatives to better understand the disease and become more familiar with diagnostic procedures. Any increased knowledge of treatment options serves to empower patients and give them the confidence to deal with their disease in an informed manner, while also supporting practical discussions with doctors and therapists.

Another aim of these patient guidelines is to show individuals how they can live better with nephropathic cystinosis and get to grips with practical problems when managing symptoms of or taking medication for this disease. Herein, we gain insights from patients' many years of extensive experience, as this patient version was written by patient representatives (patient and parents of patients).

It is important to emphasise that content from the guidelines for the management of nephropathic cystinosis was used as the basis for this patient version. Additional comments on any recommendations from the guidelines are included, where useful. All recommendations and comments from the patient expert group are clearly marked as such.

We strongly advise against making any changes to prescribed medication(s) or treatment(s) without prior consultation with treating physicians. However, these patient guidelines have been developed in conjunction with the clinical practice guidelines and can therefore be used as the basis for constructive discussions between patients and their treating physicians.

The chapters in these patient guidelines follow a clear structure. In some sections you will find text in a box which comes directly from the clinical practice guidelines, along with specific explanations. Most chapters contain a section with hints for patients and their families. Further

information can be found in the Appendix. Please contact the European or national patient organisations or visit their homepages for any specific questions.

Please be aware that these patient guidelines should be seen as a dynamic 'work in progress'. We welcome any comments or suggestions that could be incorporated into future updates.

What is cystinosis?

Cystinosis is a rare metabolic disorder caused by mutations in the *CTNS* gene (encoding for cystinosis) and is inherited in an autosomal recessive manner. This means that in most cases both parents carry at least one non-working copy of this gene and then pass it on. Therefore, the child develops cystinosis if it inherits two non-working copies of the gene.

Cystinosis causes an accumulation and crystal formation of the amino acid cystine in some cells of the body because the cell membrane is not permeable to it (and therefore it cannot leave the cell) – this leads to cell death and other pathological processes, resulting in a disease that affects multiple organs and is difficult to manage. The incidence of cystinosis (= how often it occurs) is approximately 1 in 100,000–200,000 live births and, in Europe, 10–15 new cases of cystinosis are diagnosed every year.

There are three distinct forms of cystinosis:

- Infantile or classic nephropathic cystinosis: This is the most common form of cystinosis (95% of cases).
- Juvenile nephropathic cystinosis or late-onset cystinosis: This type of cystinosis shows most of the features of infantile cystinosis, but the first symptoms do not appear until a later age (5% of cases; adolescence or older).
- Ocular cystinosis: This occurs only in adults and causes damage to the eye due to the formation of cystine crystals. Further symptoms of cystinosis are typically not expected in these patients.

The kidneys are the first organ to be affected by nephropathic cystinosis and can be badly affected. At the beginning, children are very thirsty, drink a lot, and have excessive urination. If left untreated, nephropathic cystinosis leads to kidney failure (need for dialysis or kidney transplantation) within the first decade of life. Other possible symptoms of this type of cystinosis include photophobia (sensitivity to light), soft bone (rickets) and muscle weakness, and reduced growth.

In adolescents and adults with nephropathic cystinosis, thyroid issues and fertility issues can occur. Some patients develop pancreatic insufficiency, diabetes, or fatigue syndrome in adulthood. If left completely untreated, people suffering from infantile or juvenile cystinosis die in childhood or adolescence.

Cysteamine therapy has considerably improved patient quality of life and increased life expectancy in patients with cystinosis. Cysteamine reduces the accumulation of cystine in cells, with early and consistent cysteamine therapy delaying and/or reducing the occurrence of many symptoms. The need for dialysis and kidney transplantation can be delayed until patients are in their early 20s or even later depending on when cysteamine therapy started and how well the patient adheres to this medication.

Clinical symptoms and diagnostics

Cystinosis is a rare disease with initial symptoms being non-specific and often not taken seriously enough. While not all symptoms necessarily occur, the symptoms listed below are the most common.

Infantile nephropathic cystinosis

In most patients with infantile nephropathic cystinosis, the first symptoms appear between 6 and 24 months of age. These can include:

- failure to thrive, i.e. low growth after normal size at birth.
- excessive thirst and little appetite for any food, although some children have a craving for salt (e.g. licking salt off pretzel sticks).
- high urine output, possible constipation, and unexplained fever episodes due to dehydration.
- nausea and vomiting without reason.
- slowness to crawl or walk which can be due to rickets (softening of the bones) and typically improves when on treatment.
- unexplained tiredness and listlessness.
- easy overheating due to lack of sweating or low sweat capacity.

Most children with cystinosis are diagnosed between the ages of 6 months and 2 years. Where symptoms have presented earlier, some irreversible kidney damage will have typically already occurred (i.e. this cannot be cured or reversed). Beginning therapy for nephropathic cystinosis immediately after diagnosis can help to delay any further damage to the kidneys.

Juvenile nephropathic or late-onset cystinosis

This form is even more rare than infantile cystinosis and affects the kidneys and other organs. Patients do not typically show symptoms of juvenile nephropathic or late-onset cystinosis until they are around at least 10 years old.

Ocular cystinosis

In ocular cystinosis, which only occurs in adults, only the cornea is affected. Due to the rarity of this form of cystinosis, a urine and kidney examination is recommended to rule out kidney involvement (which would otherwise indicate nephropathic or juvenile, and not ocular, cystinosis).

Diagnosis

Cystinosis is usually diagnosed in stages. Depending on the symptoms, blood and urine are analysed first. In most cases, laboratory values show signs of renal Fanconi syndrome

(generalised malfunction of the proximal tubules of the kidneys), which is recognised by increased losses of water, electrolytes (e.g. bicarbonate, sodium, potassium) proteins and glucose in the urine. The second step is to discover the cause of this Fanconi syndrome. Cystinosis is the main cause of Fanconi syndrome in children and adolescents.

If Fanconi syndrome is diagnosed, measuring cystine content in white blood cells (leucocytes) and/or genetic testing of DNA for mutations in the *CTNS* gene is strongly recommended. Both methods can confirm the diagnosis of cystinosis. If the results of the cystine test and the DNA test do not match, the patient should be examined in a specialised cystinosis centre.

In the case of juvenile cystinosis, it can happen that Fanconi syndrome is recognised and treated correctly, but cystinosis is not recognised.

If no blood test is available, an alternative way of diagnosing cystinosis is to examine the eyes for cystine crystals on the cornea. However, an eye examination is not reliable in children aged under 24 months of age. In very young children, crystals on the cornea are not easy to find with a slit lamp examination or may not be present at all.

Newborn screening and genetic counselling

While there is no cure for cystinosis, getting the earliest possible diagnosis and immediately initiating cysteamine can help maintain kidney function for longer, along with significantly delaying kidney failure and other cystinosis-related issues in children.

Where an older child is diagnosed with cystinosis, older siblings should be tested as well, and younger siblings should be diagnosed immediately after birth. Research has shown that if a child with cystinosis is diagnosed at birth and starts cysteamine within the first weeks of life, it is more likely to maintain good kidney function well into adolescence and young adulthood, with reduced risk of damage to other organs.

The patient expert group strongly recommends that all siblings of a child with cystinosis be tested immediately at birth or as soon as possible. In many countries, a heel prick test is done a few days after birth, with the parents' permission. This involves taking a sample of blood from the baby's heel and collecting it on a piece of card which is then analysed for a number of diseases. Cystinosis is not yet part of the newborn screening programme in any country, but this might happen in the coming years.

Here's what the guidelines say:

We recommend establishing newborn screening for cystinosis.

Remark: *Until another reliable method (metabolite) is available, genetic screening can be recommended.*

We recommend initiation of cysteamine therapy in patients with cystinosis as soon as a diagnosis is made.

It is also possible to test the unborn child for cystinosis during pregnancy. This test can be considered if an older sibling has cystinosis or if cystinosis has already occurred in the immediate family. As there are some risks for the foetus associated with this test (called an amniocentesis), expectant parents should consult with their doctors first. Prior to testing, genetic counselling should be offered and the option to terminate the pregnancy should be available in countries where this is possible.

Professional genetic counselling is recommended for a couple if any other member of their families have been previously diagnosed with cystinosis. As part of this, both partners will be offered a genetic test to see whether they are carriers of the disease. When they have this information, they can then decide whether they want to take the risk of planning a pregnancy despite the possibility of having a child with cystinosis. If only one of the two partners is a carrier of the disease, their child will not have cystinosis but may be a carrier for the condition.

Treatment

Preliminary remarks

The patient expert group recommends that patients be cared for by a multidisciplinary team in a specialised centre for cystinosis in cooperation with their local family practice. This increases the chance of successful treatment and a better quality of life for those affected (see chapter: 'Integrated care').

- Cysteamine in either format is the only active substance that can be used to treat cystinosis and slow down the progression of the disease. Every patient should have access to this medication (see chapter: 'Cysteamine therapy').
- The use of new therapies (e.g. gene therapy or novel medications) should be utilised in the long term in all countries, if shown to be successful in clinical studies.
- Immediately after diagnosis of cystinosis (or as soon as possible), all families should be offered socio-psychological counselling or support. This option should be made available to all patients throughout life, regardless of their disease stage.
- In addition, all families should be given information about cystinosis patient organisations and advised to make contact with them (see Appendix).

The information on the medical treatment of cystinosis in these patient guidelines is supplemented by tips and suggestions from the practical experience of affected patients and families. These can be found at the end of each chapter. A table with information on medication can be found in the Appendix at the end of these guidelines.

Cystinosis is a life-long condition, and symptoms may vary over time. Certain symptoms may present at a certain age or become increasingly challenging at key points in a person's lifetime. If cysteamine therapy is started at a very young age and continued consistently throughout life, some symptoms may be mild or possibly might never occur. All possible symptoms will be outlined in these patient guidelines.

The overview below is not complete (see chapter: 'Integrated care'), but shows how many specialised disciplines may be involved in the treatment of cystinosis. All these disciplines will be mentioned in this guideline. Patients should have the opportunity to see specialists in all these clinical fields should questions arise. The patient's lead doctor, typically a kidney specialist, can advise.

Infancy and early childhood	Puberty/Adolescence/Adulthood (additional)
• Genetics • Nephrology (kidneys) • Ophthalmology (eyes) • Gastroenterology (stomach, gut) • Nutrition/dietary advice • Neurology (nerves, muscles) • Endocrinology (hormones, e.g. growth hormone) • Orthopaedics (feet, legs, spine) • Physiotherapy • Occupational Therapy • Speech and Language Therapy • Counselling and Psychology (Patient, parents, and siblings)	• Endocrinology (sexual maturation, fertility) • Gynaecology • Pulmonology (lungs and breathing) • Cardiology (heart) • Professional guidance through transition

Cysteamine therapy

Cysteamine is the only medication that slows down or prevents damage to organs in individuals with cystinosis.

Here's what the guidelines say:

We recommend the initiation of cysteamine therapy in patients with cystinosis as soon as a diagnosis is made.

The earlier patients begin cysteamine treatment, the better the preservation of kidney function. Cysteamine is used as a treatment for both of the most common variants of cystinosis, infantile nephropathic cystinosis, along with the rarer juvenile cystinosis.

Cysteamine is available in three different formulations – not all of them are available in all countries.

- Immediate release (IR) form (Trade name in 2024: Cystagon®).
Available in capsule form that opens in the stomach. This type of cysteamine must be taken four times per day, at exactly six-hourly intervals (even at night).
- Delayed release (DR) form (Trade name in 2024: Procysbi®).
Available in capsule format and as sachets in some countries. The coating on the medication causes the active ingredient to have a delayed release in the gut. This type of cysteamine must be taken every 12 hours.
- Mercaptamine powder is weighed and filled into small bottles or syringes by the local pharmacy on the advice of the nephrologist. It must be taken four times per day, at exactly 6-hourly intervals (even at night). Important note: It is important to mix the powder with liquid just before taking it. Cysteamine is not stable and may stop working after a few hours.

Here's what the guidelines say:

We do not recommend favouring one formulation of cysteamine over the other. Cysteamine DR and IR are equally effective for lowering white blood cell cystine levels in clinical studies.

We recommend choosing the cysteamine formulation based on the individual patient's needs.

Remark: Cysteamine DR may improve treatment adherence and quality of life in some patients.

The choice between DR and IR formulations of cysteamine is a decision for parents and patients in consultation with their doctor, but will depend on their availability in specific countries.

Because cysteamine DR is given every 12 hours, the ability to sleep through the night without having to wake up for medication is an important benefit for some patients, along with their parents. For children, not having to take cysteamine at school can also be an advantage. One disadvantage may be that if a dose of cysteamine DR is missed, a long period may then occur between doses, which could be detrimental to the patient's health should it occur regularly. Since cysteamine IR has to be taken every 6 hours exactly, a missed dose would occur over a shorter period of time.

Both formulations of cysteamine can cause gastric side effects, such as nausea and vomiting, in some patients. Some patients try both formulations of cysteamine before they make a decision.

Dosage

The following dosing recommendations for cysteamine currently apply (July 2024).

Here's what the guidelines say:

Remarks:

- Cysteamine therapy should be given to all patients (infantile nephropathic, juvenile nephropathic cystinosis) regardless of age and transplant status.
- Optimal dosage of cysteamine is patient dependent and should be determined (where possible) on cystine depletion.
- The recommended cysteamine dose for cysteamine IR according to the manufacturers is as follows:
60 to 90 mg/kg/day or 1.3 to 1.95 g/m² body surface divided in four doses.
- The recommended dose for the DR formulation is 80% of the IR dose, divided into two doses administered every 12 hours.
- Initiation of cysteamine therapy after diagnosis: Cysteamine should be initiated at 10 mg/kg/day and increased over a period of six weeks to reach the required dosage (calculated as mg/kg/day). *This dose increase can be accelerated, if tolerated.*

Weight-adjusted cysteamine dosage:

Up to 10 kg: 80–85 mg/kg/day

10–17 kg: 80 mg/kg/day

17–25 kg: 70 mg/kg/day

25–40 kg: 60 mg/kg/day

40–50 kg: 50 mg/kg/day

This table provides guidelines for the doses that can be used. In centres where determination of intraleukocyte cystine concentration is not available, this table provides guidelines for recommended doses.

These doses can be increased depending on the clinical tolerance of the patients.

However, the dose should never exceed 90 mg/kg/day.

Cysteamine should be started at a low dose of 10 mg/kg/day to avoid stomach pain and severe gastrointestinal side effects. The dose should be gradually increased over 6 weeks to reach the optimal dosage. The child should be carefully monitored while increasing the dose of cysteamine.

In centers where leukocyte cystine levels are not available, the dose of cysteamine can be adapted based on clinical tolerance, as long as it does not exceed 90 mg/kg/day or 1.95 g/m²/day, with a maximal dose of 2.0 g/day, according to the manufacturer's instructions.

Whenever possible, doses of cysteamine should be adjusted based on trough leukocyte cystine levels. In principle, the lowest possible leukocyte cystine level should be aimed for, within the above dose limits. In some centres however, the dose of cysteamine is increased up to 3.6 g/day when adult patients cannot achieve adequate leukocyte cystine levels.

Cystine blood test

The cysteamine dose is related to the level of cystine in leukocytes. As the child grows, the dose of cysteamine must be increased based on the child's weight/body surface area. The cysteamine dose should be increased slowly to reduce the risk of stomach upset.

For best results in testing for cystine, the timing of the blood draw for this test is important.

- When the patient takes cysteamine IR, blood should be taken 6 hours after the last dose.
- When cysteamine DR is taken, blood should be drawn 12 hours after the last dose.

The cystine blood test should be repeated every 3–6 months once the optimal dosage has been reached. If the outcome of the test does not meet the expected levels, check back with the clinic (i.e. laboratory). If necessary, the test should be repeated before making any further therapeutic decisions.

Here's what the guidelines say:

We recommend using either pure granulocytes or mixed leukocytes for the determination of the cystine level. We suggest using preferably granulocytes.

Remark: *The patient should be monitored consistently using the same method (pure granulocytes or mixed leukocytes).*

Cysteamine side effects

Cysteamine has a range of side effects that can affect each patient in different ways. Sometimes it is not clear if symptoms relate to cystinosis itself, cysteamine, or even other medication or events.

If any of the following symptoms occur, seek medical advice immediately:

- Severe headaches
- Severe gastrointestinal symptoms (e.g. vomiting or diarrhoea)
- Bruise-like lesions (which can look like bruises or blood blisters on elbows or knees and/or stretch marks on any part of the body).

These symptoms can indicate rare, but serious, side effects.

Patient recommendations: Cysteamine Intake and tolerability

Here are some ideas and tips from the patient expert group on how to manage use of cysteamine and potential side effects. These tips may work for some patients and not others, so it may be helpful to try new ideas in consultation with the healthcare team.

Side effects may improve over time as the child grows and gets used to the medication.

When cysteamine therapy (in any form) is first prescribed, it is most important that this should be started at a low dose and then increased very slowly. This remains important when increasing the dose as the child grows.

Effective time management is crucial for taking cysteamine as prescribed. Patients and their parents should carefully consider which times best fit into their daily routine (every 6 hours for cysteamine IR and every 12 hours for cysteamine DR) and aim to adhere to these times as consistently as possible.

Suggestions for consideration

- For most patients, cysteamine will be provided as capsules. Most adult patients can take the capsules by mouth. If cysteamine capsules need to be opened so that the contents can be poured into a liquid to drink or be administered into syringes, assistance from the medical team or pharmacist should be sought to ensure correct procedures are followed.
- Small amounts of cysteamine are difficult to measure, e.g. when a small child starts treatment and has to take 20 mg in one dose, but the content of the capsule contains a 50 mg dose. Pharmacists can provide help here and give pre-measured amounts of

powder or pellets in syringes or glass vials, one for each intake. These can be filled with a little water, juice, broth, or milk to provide each dose as a drink or liquid for administration via a feeding tube. (See table 'Medication' in the Appendix).

- When starting cysteamine, the dose should be slowly increased until the full prescribed dose is reached. This will reduce the risk of stomach upset. If any stomach upset occurs, the dose should be reduced until this settles down.
- If there are difficulties tolerating the prescribed dose of cysteamine, alternative options should be discussed with the doctor. It is important to take the correct dose each day (see Table above).
- Cysteamine can be discontinued for 1 or 2 days in the event of a gastrointestinal infection. In this case, it is more important to take all other medications (salts, electrolytes or immunosuppressants). In the event of any severe health problems, a clinician should be consulted.

Administration of Cysteamine IR (Cystagon®)

- Cysteamine IR and cysteamine solution can be given with or after meals, or with milk or yoghurt or a snack, depending on the time of intake.
- Cystagon® capsules can be opened, and the content be sprinkled in a drink or over food. This should be consumed within 30 minutes.
- Tube feeding is possible. Cysteamine IR can be mixed with any liquid. Remark: For tube feeds, cysteamine should never be given continuously over a long period of time (e.g. overnight with a cyclor).

Administration of Cysteamine DR (Procysbi®)

- Cysteamine DR is best taken at least 1 hour before or 1 hour after a meal. If fasting is not possible, patients should eat a small amount (~100 g) of food (preferably carbohydrates) during the hour before and after the Procysbi® dose.
- Cysteamine DR should be not taken with food rich in fat or proteins like milk (dairy products), or with frozen food like ice cream. It should not be taken at the same time as sodium bicarbonate. A 30-minute interval should be allowed between each use.
If the patient is unable to swallow Procysbi® capsules, the content of the capsules can be sprinkled into 100–150 mL of orange or apple (acidic) fruit juice. Mix gently for 5 minutes using a dosing syringe or covered cup. Consume immediately or refrigerate for no longer than 30 minutes. Alternatively, capsules can be opened, and contents can be sprinkled onto 100 g of apple sauce, and thereafter stirred gently. This should be consumed immediately or refrigerated for no longer than 2 hours.
- Cysteamine DR could theoretically be given through a feeding tube, but as the pellets do not fit well through all commonly used gastric tubes (e.g. percutaneous endoscopic gastrostomy [PEG]), the healthcare team should be asked for advice.

Further information can be found on the respective companies' home pages.

Patient recommendations: Cysteamine side effects

Cysteamine has many side effects. Many patients experience stomach pain and strong nausea after taking cysteamine, especially in combination with other medications. This can be particularly bad in the first few years of treatment, but it usually gets better.

In addition, a strong smell of sulphur may develop, potentially causing unpleasant body odour and bad breath (halitosis) in patients. There are many suggestions to reduce the odour, but no evidence-based data are available to confirm the best approach. It is worth trying different ways of managing this odour to see what works best.

Reference to the 'Medication' section in the Appendix should be made for an overview of the types of medication that can be taken alongside cysteamine.

Masking the taste and associated nausea

- To mask the taste, Cystagon® capsules can be taken with chilled water, various juices, broth, or tea. Procysbi® should be taken with orange or apple juice.
- Taking cysteamine with camomile tea instead of water or juice can help to manage stomach pain. This could be a natural stomach protector, especially for small children, and can be used with a PEG tube as well.
- Nausea may also be due to an interaction with sodium bicarbonate or Shol's solution. In most cases it is possible to postpone the time of intake of these medications.
- Cysteamine should be not taken again immediately after vomiting as this usually provokes further sickness.

Dealing with the strong smell

- If possible, cysteamine should not be taken on an empty stomach. For cysteamine IR, it may help to eat yoghurt, cheese, or other dairy products. Cysteamine DR should not be taken with dietary products (see above).
- Some over-the-counter products can help to mask the strong smell of cysteamine. These include high-dose chlorophyll in tablet or liquid forms in high dosage, vitamin B2, and wheatgrass. These approaches should always be discussed with the treating doctor before trying them.
- Showers, deodorants, body sprays, perfumes or breath fresheners can help mask the smell.

Chronic kidney disease (CKD)

Fanconi syndrome

The infantile form of cystinosis usually presents at the age of 6 to 24 months with renal Fanconi syndrome. This does not necessarily mean that a correct diagnosis has already been made. Unclear symptoms, such as growth disorders (failure to thrive), in combination with excessive urination and drinking of water, or unusual and significant tiredness are often misinterpreted.

Cystinosis is the most common cause of Fanconi syndrome in children. The symptoms as described in section 3.1 are typical, but do not necessarily occur in all children. However, they are quickly noticed by parents and are always a warning sign, even after treatment has begun.

Blood tests reveal the dramatic loss of electrolytes, including metabolic acidosis (hyperacidity of the blood) in conjunction with the loss of sodium, potassium, calcium and phosphate, protein, and carnitine, along with low uric acid levels.

Treatment

Renal Fanconi syndrome is treated with adequate electrolyte and fluid replacement and nutrition. This approach is crucial for the child's wellbeing and growth.

Here's what the guidelines say:

We recommend adjusting electrolyte (sodium, chloride, phosphate, calcium, potassium, magnesium) supplementation to achieve serum levels in the (lower) normal range in all patients with cystinosis.

We recommend monitoring of electrolyte levels regularly, at least every 2 to 3 months, depending on age, clinical situation and adherence.

We recommend alkali supplementation, as needed, in patients with nephropathic cystinosis.

We recommend monitoring serum bicarbonate levels regularly in all patients with nephropathic cystinosis and metabolic acidosis secondary to renal Fanconi syndrome or CKD, at least every 3 months.

Regular monitoring of blood levels (electrolytes and bicarbonate) is absolutely essential. Children up to the age of 6 years old should have a regular check-up every 2 to 3 months, while this should be every 3 to 4 months for older children, adolescents, and young adults.

Patients with cystinosis need a healthy, balanced diet to help manage their Fanconi syndrome. The diet should have an adequate calorie content and provide sufficient amounts of fluids and salts. All patients should be supervised by a paediatric dietician (see chapter: 'Nutrition').

For many children, vomiting, and loss of appetite can be a significant issue. A gastrostomy tube may be required to ensure enough calories are consumed. The caloric intake should be 100% of the weight requirement. There is no evidence that a higher intake of calories leads to better development or growth. The gastrostomy tube can also be used to administer additional fluids and medication (see chapter: 'Tube feeding').

The appropriate and timely use of medication is key to the effective management of cystinosis. Patients must follow a medication schedule which may involve taking several medications that could interact with each other. Thus, managing these medications can be difficult. Each patient

and family have to find their own way and they should consider asking their healthcare team and/or a dietitian for advice.

Further information on handling medication can be found in the chapter 'Cysteamine therapy'. See the Appendix for a summary of which medications can be combined.

Polyuria

Children with cystinosis typically have polyuria (excessive urination). This is a feature of Fanconi syndrome that only resolves following a kidney transplant. Monitoring the amount of urine produced in patients with cystinosis is desirable.

Reducing fluid intake in children with polyuria is not an option. This approach would not reduce the amount of urine but could increase the risk of dehydration. Medication to reduce fluid loss (e.g. indomethacin) can be helpful, but this also has side effects.

Here's what the guidelines say:

We suggest the administration of indomethacin in children with nephropathic cystinosis who have severe uncontrolled Fanconi syndrome.

Remarks:

- *The combination with proton pump inhibitors (PPI) treatment can prevent side effects in the gastrointestinal tract, such as gastritis and gastric ulcers.*
- *In children with nephropathic cystinosis, treatment with indomethacin should be discontinued as soon as possible once the Fanconi syndrome is well adjusted.*
- *Indomethacin should not be used in older children and adults with nephropathic cystinosis and impaired renal function.*
- *Indomethacin should be discontinued in patients with nephropathic cystinosis if patients show deterioration in renal function, are unable to compensate for fluid loss, or are in a sick/dehydrated state.*
- *Regular monitoring for nephrotoxicity, including determination of urine volume, renal function (glomerular filtration rate), electrolytes, bicarbonate, and haemoglobin levels (at least every 3 months, depending on patient age and drug adherence) is necessary during treatment with indomethacin in patients with nephropathic cystinosis.*

Incontinence is a substantial problem for children with cystinosis and their families. Some may lose control of their urinary functions, even if they were previously toilet trained without problems. Most of them achieve control in the daytime before they enter pre-school.

Night-time incontinence is a big problem for patients with cystinosis and their parents. In children with cystinosis, this can last until puberty. Here are some suggestions from patient experts on how to make nocturnal incontinence easier to bear:

- Importantly, no child is 'voluntarily' or 'intentionally' incontinent. All children feel uncomfortable with their incontinence, and many are ashamed that they do not realise when they need to go to the toilet at night, even at a school age.
- Patience is essential here. At some point, every child will be 'dry' at night. It helps to realise that many physically healthy children are just not ready for this until they reach school age. For many children, this is not until the age of 5 or 6, and possibly even older.
- With an older child, one parent can take the child to the bathroom during the night. A good rhythm for use of the bathroom is once before the parents go to bed, then at the time of the nightly medication.
- If possible, parents should take turns getting up at night so that one of them can get sufficient sleep every other night.
- Over time, children will typically learn to wake up at a certain time and then realise that they need to go to the toilet.
- Most children need to drink at night. Small children often have a bottle in their bed, which they just have to reach out for. For older children, it can be a good idea to set the bottle or glass beside the bed. The child will wake up and get up because they are thirsty and then realise they need to go to the bathroom.
- Bed-wetting alarms have proved effective in many cases. These alarms are worn at night and make a noise as soon as the smallest amount of urine is detected, alerting the child to wake up. Again, this process helps the child to learn to wake up during the night and realise that they need to go to the toilet.
- Sleepovers with friends or sleepover parties at nursery or school can be a challenge. Some children do not sleep as soundly as normal when they are away from home and are more likely to wake up. Other children have to individually decide who they trust enough to risk planning an overnight visit.
- Parents should know that scolding, regret, reproaches or even just 'being sad that it still does not work' is a major stress factor for their child, which in turn favours bed wetting. Patience and calmness are the best way to see this temporary, although often long, phase through to a normal state.

Kidney replacement therapy

Kidney replacement therapy (dialysis and kidney transplant) is unavoidable and vital for most patients with cystinosis when kidney function becomes very limited. Most young patients with cystinosis have access to a regular supply of cysteamine and so will not need renal replacement therapy until they are 16 years of age or older, if they take their medication as prescribed.

Symptoms of declining kidney function include deteriorating blood values, a general unwell state, fatigue, and sometimes nausea and headaches. As there are good guidelines on both dialysis and kidney transplantation (see: 'Links and addresses'), full details will not be included here.

The progression to kidney failure (CKD stage 5 or less than 15% of a normal kidney function) is typically slow. The decision when to start dialysis or when to schedule a transplant (living

donor) depends on the patient's current condition. Patients are placed on a waiting list for a post-mortem kidney donation (donation of a kidney from a deceased donor) or, if possible, undergo living-related kidney transplantation. In the latter case a kidney is usually donated by a healthy parent or a spouse (in adults) and may also allow pre-emptive (without prior dialysis) transplantation if plans are made in advance. In some countries, pre-emptive transplantation is also possible for children undergoing deceased donor kidney transplantation. However, the waiting time maybe too long in many cases to reach this goal.

It is recommended that patients are transferred to a kidney transplant centre before reaching CKD stage 4 (less than 25% of kidney function) to get advised about these possibilities and avoid unnecessary dialysis in case of the possibility of a pre-emptive living-related kidney transplantation. This allows to discuss all options thoroughly with the transplant team in order to reduce any uncertainty and/or anxiety. It is also recommended to seek advice from members of the socio-psychological team in parallel with any clinical consultation(s).

Dialysis

If pre-emptive kidney transplantation is not possible, dialysis is the only option. Not much needs to be considered with regards to the underlying cystinosis.

All cystinosis-related extra-renal organ problems (e.g. in muscles or eyes) have to be treated. Thus, treatment with cysteamine should be continued. Cystine levels in dialysis patients may be different due to the removal of cysteamine during dialysis, although there are no recommendations to routinely change the dosage of cysteamine.

Here's what the guidelines say:

We suggest that the dose of cysteamine should not be routinely adjusted in patients with nephropathic cystinosis undergoing chronic dialysis treatment.

Two types of dialysis are possible: haemodialysis and peritoneal dialysis. Both procedures have pros and cons, are equally successful, and both require preparation. In some countries, only one or the other type of dialysis may be available. The choice of kidney replacement procedure is made by the patient/ family after counselling by the dialysis team based on:

- health or personal reasons for or against the procedure
- wishes of the patient and family
- living conditions.

Children and adolescents should also have a significant say in the decision to undergo dialysis. During dialysis, many young people learn a lot about their body and their illness and many experience independent interaction with the treatment team and medical technology for the first time.

Haemodialysis

Haemodialysis is usually performed three times a week in a dialysis centre. In some cases, 'home haemodialysis' is also possible, although a minimum of two relatives of the patient should be well trained and confident to support this procedure.

A shunt is placed before the start of dialysis. This means that an artery and a vein are joined to form a fistula in a small operation on the arm. It takes several weeks before the shunt can be used. Alternatively, a permanent dialysis catheter can be placed in a jugular vein, in case creation of a shunt is not feasible. Through this access, blood is then directed into the dialysis machine for purification through a tube that is connected during the procedure. The cleaned blood returns to the body through the closed circuit.

Patients planning to travel for more than 2 or 3 days should inquire about available dialysis centres in advance.

Peritoneal dialysis

Peritoneal dialysis is carried out at home. Here too, one or two relatives need to be well trained. Adolescents and adults also learn how to dialyse themselves.

The catheter (a thin plastic tube) for this dialysis is inserted into the abdominal cavity during an operation. Training in this form of dialysis must be provided at the outset, and this typically occurs in the clinic.

Dialysis fluid from a bag is passed through the catheter into the abdominal cavity several times a day or during the night, where it remains for several hours. This fluid is used to purify the blood via the peritoneum. After a few hours, the fluid is drained back into a bag and new fluid is added. During draining and filling, the patient must lie, sit, or stand, although free movement is possible.

Based on the experience of patient experts, travelling with this form of dialysis is possible, although a great deal of preparation is required.

Sport during peritoneal dialysis is possible, but contact sports, tennis, badminton, or similar activities should be avoided, as the peritoneum can be damaged by the large amount of fluid during sudden 'stop and go' movements.

Transplantation

Transplant outcomes in patients with cystinosis are generally very good. There are no known interactions between immunosuppressive drugs and cysteamine. As soon as the patient is able to eat and drink after the transplantation, use of cysteamine should be resumed. Even though the transplanted kidney no longer stores cystine and is not affected by cystinosis, all other organs in the body must continue to be protected.

Here's what the guidelines say:

We recommend kidney transplantation in patients with kidney failure due to cystinosis, if possible pre-emptive and if not available haemodialysis or peritoneal dialysis as available, indicated and according to current guidelines.

Remark: *In addition to the evaluation already performed on any kidney transplant candidate, the extent of cystinosis extrarenal organ involvements should be evaluated.*

Post-transplant care is identical to that of other kidney recipients, with the exception of the need to monitor for systemic effects of cystinosis.

Life-long use of immunosuppressants is necessary to prevent graft rejection. Side effects of immunosuppressive treatment after kidney transplantation may include increased susceptibility to viral and mycotic (fungal) infections, malignancies, diabetes, and fatigue or migraine-like headaches.

After transplantation, the native kidneys may eventually stop working completely, so that the Fanconi syndrome disappears without the need for kidney removal.

Here's what the guidelines say:

We suggest considering nephrectomy prior to kidney transplantation in cystinosis patients with severe polyuria and/or severe proteinuria.

Remark: *As a rule, a unilateral nephrectomy is performed first; if this appears insufficient, the second kidney is removed, preferably during a transplant operation.*

Problems of the gastrointestinal tract

Patients with nephropathic cystinosis often have problems in the upper and lower gastrointestinal tract. There may be many reasons for this which are not always clearly defined. This can lead to malnutrition with serious consequences, particularly in younger children.

Treatment with cysteamine may cause nausea, vomiting, diarrhoea, or abdominal pain. Cysteamine produces increased gastric acid which, if untreated (see below), may cause stomach ulcers. The many different medications used to treat Fanconi syndrome can also cause stomach pain and vomiting, particularly in younger children.

The large amounts of fluids that non-transplant patients have to drink contribute to a feeling of fullness, so that other foods are perceived as not being needed. Drinking too much fluid at once can also lead to reflux and, therefore, vomiting.

Problems with swallowing solid food also occur more frequently in children and may recur in some adults for a variety of reasons.

The psychological impact of cystinosis is further amplified by the gastrointestinal issues associated with the disease, with psychological factors playing a significant role alongside other challenges.

For these complex and lifelong problems, patient experts strongly recommend that treatment and disease management strategies should be implemented and supported by an interdisciplinary team comprising members from nephrology, gastroenterology, endocrinology, psychology, dietetics specialist advice, and speech therapy.

Treatment of stomach problems

Here's what the guidelines say:

We suggest the use of PPIs (drugs that inhibit the formation of stomach acid) in patients with cystinosis who have gastrointestinal symptoms such as frequent vomiting and/or nausea, abdominal pain, and reflux.

Remarks:

- After the gastrointestinal symptoms have subsided, discontinuation of the PPI should be considered.
- Caution: Side effects of PPIs such as vitamin B12 deficiency may occur.
- In patients taking cysteamine in ER capsules, the use of PPIs may impair the effect of the sustained release.
- Patients taking PPI should have the need reviewed at least every 6 months. If discontinuation of the medication is indicated, a gradual reduction of the medication is recommended.

Patient experts recommend trying other ways to initially reduce stomach pain and its consequences, particularly in children:

- Liquids should be consumed slowly, ensuring they are not too cold, and the intake of carbonated drinks should be limited.
- Food that is easy to swallow, such as soups, broth, or yoghurt, should be preferred, and meals should be eaten slowly.
- Medication should not be taken on an empty stomach. Patients taking Cysteamine DR might need special advice.
- The use of camomile tea, a hot water bottle, and occasionally home remedies may provide relief.
- Simple medication for nausea, used in consultation with a doctor, can be effective.
- It is important to acknowledge that illness is never intentional.

Further recommendations can be found in the chapters: 'Nutrition', 'Tube feeding', and 'Medication'.

Nutrition

Food intake and diet composition is an important issue for all patients with cystinosis. Malnutrition is dangerous and causes failure to thrive (e.g. growth retardation and general physical weakness) in children. Malnutrition may become an important issue again in adolescents and adults facing deteriorating kidney disease.

The clinical guidelines can only set important targets here. Patients and their families must try to ultimately decide what is effective for them. It is very important that even the youngest patients have a say in this. In addition, you should stay in regular contact with your medical team in order to recognise a potential nutritional crisis – but also to celebrate food intake/dietary successes.

General nutrition guidelines exist for adults and children with CKD. Clinical practice recommendations have also been published for children. The most important advice is to use age-appropriate screening tools and treatment approaches for the prevention, early detection, and treatment of malnutrition in patients with cystinosis.

While this may sound very complicated, for parents it simply means recognising the importance of taking their child to regular outpatient clinic appointments and seeking timely advice from a registered medical nutritionist.

The clinical guidelines recommend the following observations or examinations:

- Children up to the age of 3 years should be examined every 3 months and older children every 6 months with regards to their nutritional status.
- Keeping a 3-day food log every 2–3 months shows what is really being consumed (food and drink).
- Laboratory investigations should be part of every physical examination as much as the measurement of weight and height.

The aim of such advice is to improve caloric intake through proper nutrition, prevent malnutrition, and possibly even compensate for the loss of salts and electrolytes due to kidney disease. In this way, health can be maintained for longer and the patient's general condition may even be improved.

Further goals are to improve symptoms in the gastrointestinal tract and later adapt the diet for patients with swallowing difficulties.

Patient experts have compiled many practical recommendations on this topic. All of these have been tried and tested – most work, but not for everyone. Ultimately, patients and their families have to decide what is possible and/or feasible.

Basic information for parents

- Freedom to access water is essential.
- Children with cystinosis are allowed to eat anything and as much of it as possible!

- Food or eating should not become a topic of contention. “If you don't eat, then...” discussions don't lead anywhere. Access to fluids should never be made dependent on eating a certain amount.
- Mental discomfort also increases stomach pain and can lead to vomiting.
- A balanced diet and several meals a day are important. It helps some children if they are offered small snacks that can be swallowed quickly (yoghurt, quark, fruit puree, etc).
- Children should be involved in shopping and preparing meals from an early age. Many are curious and interested, like most children. They like to help with cooking, but it is usually the others at the table who have to eat it.
- Occasionally transforming a meal into an engaging 'event' can be beneficial, such as using a straw for drinking, eating with a fork instead of a spoon, or incorporating special plates.
- Most children with cystinosis will eventually learn to eat normally; while many do not completely forget how to eat, the quantity consumed is often insufficient.

And what is recommended to drink and eat now?

- Children can eat and drink anything they like.
- Some children love milk.
- A small bottle of water can be placed in the bed of a child aged 2 years or older to help quench their thirst during the night.
- Children with cystinosis have strange food preferences (when they eat)! Most of them like to eat salty, sour, and spicy foods, or at least nibble on them. Examples of these include salt sticks (with lots of salt), pickled gherkins, mustard or spicy herb cheese (instead of jam), and pasta with bell pepper sauce (instead of white cheese casserole). Many children with cystinosis also like to eat sausage or meat. Parents should know that these foods can also replenish a (small) part of their child's electrolyte loss and that there is nothing wrong with it.
- There are many ways to add calories and vitamins into favourite foods (cream, pureed vegetables, meatballs with egg and pureed peppers or herbs). Even a child who only eats pasta with tomato sauce for 3 months can have tomatoes, broth, cream, cheese, and pasta every day.
- It is important to keep in mind that the child is under medical supervision. As long as they consume sufficient fluids, there is no risk, and they will not experience starvation.
- Nutrition and medication are important topics in families with children affected by cystinosis. However, they should not determine how the whole day is planned.
- If it becomes clear that adequate oral nutrition is not possible, the use of a gastric tube for feeding is recommended until oral intake becomes sufficient.

Important to know for adults

- Eating patterns may change as children grow into adolescents and adults, or after transplantation, to more closely resemble what is considered 'normal' in both quantity and mix of dietary preferences.

- Adults with cystinosis whose kidney function is deteriorating are at high risk of malnutrition. Depending on their state of health, they should seek targeted dietary advice at an early stage.
- Adults may experience increased swallowing difficulties because the onset of weakness in the connective tissue and muscles also affects the throat and pharynx. Special training with an occupational therapist or speech therapist can be helpful here.
- If food intake becomes too difficult, the placement of a feeding tube can be considered for adults to provide nutritional support.

Tube feeding

Children

The use of a feeding tube for a child with cystinosis is a question that many parents are confronted with. Before a decision is made, careful consideration should be given by parents and the treatment team as to what best meets the needs of the individual child.

Poor food intake, failure to thrive, frequent vomiting, electrolyte disturbances, large urine output, and an unquenchable thirst are the hallmarks of cystinosis in the early years. After diagnosis, many nasty-tasting medications are added to the daily routine. In many families, not only eating but also taking the medication several times a day at the right time becomes a recurring challenge. Inserting a feeding tube can take a lot of pressure off the parents and the child.

The clinical guidelines do not give a clear recommendation either for or against the insertion of a feeding tube for food and medication intake. The pros and cons should be discussed with the patient and family by the medical team.

Advantages:

- If a child consistently refuses or is unable to take medication orally, a feeding tube becomes necessary. However, the tube does not need to be used for food if the child is already eating and drinking.
- If the child's food intake does not provide enough calories, it can be increased with food supplements.
- Parents have more opportunities to give food and, above all, fluids when the child is ill.
- Older children learn to tube themselves (under supervision), but the goal should always be for the child to eat meals with the family or alongside peers at nursery or school.
- In the event of a gastrointestinal infection, inpatient treatment for intravenous rehydration can sometimes be avoided by supplying fluids via the gastric tube.

Disadvantages:

- Depending on the type of tube, inserting a feeding tube may require surgery under general anaesthetic.

- The entry point of the tube must be cared for and can become inflamed.
- In some cases, it may become difficult to wean the child from the tube after habituation.

Adults

Some adult patients with cystinosis have great difficulty swallowing due to muscle weakness. They can only chew and eat very slowly and often choke. In cases of severe malnutrition, tube feeding may also be appropriate for adults.

Such a decision should always be preceded by a detailed consultation with the treatment team, including the involvement of a gastroenterologist and speech therapist.

What feeding tubes are available?

The principle of the individual tube types is not described in detail here. However, useful patient information will be available in the gastroenterology department.

- The nasogastric tube is a very thin tube which is inserted through the nose and oesophagus into the stomach. This allows medication and tube feeding to be administered. It is not intended for long-term use if there are other alternatives.
- A PEG tube is an elastic tube that is connected to the stomach through the abdominal wall. The entrance to the tube (stoma) is in the upper abdomen and is fixed by a plate. This type of tube can only be changed via surgery. A short piece of tube hangs from the end of the tube, which also has a stopper, so that medicines and food can be fed into the stomach. The tube comes in different sizes and can also be used to feed pureed food.
- A gastric tube is similar to a PEG but is usually attached using a balloon instead of a plate, which makes it easier to change. It can be changed by the parents themselves.
- A button is a feeding tube lying flat on a patient's skin that takes the place of the PEG tube. This may feel preferable to a regular PEG tube because it cannot be seen under most types of clothing. A PEG feeding tube can usually be changed to a button after 6 weeks, once the tube opening is well-healed.

With a button, patients have more freedom, it does not get stuck, and can be changed independently by parents. It also requires much less care and results in far fewer inflamed areas.

- A jejunostomy tube (or J-tube) is a soft, plastic tube placed through the skin of the abdomen into the midsection of the small intestine. This is used in rare cases when a patient's stomach cannot tolerate food or medication at all.
- The correct choice of tube length and diameter and correct placement is very important.

Anyone can learn how to use a tube correctly and how to fix small problems themselves. There are training courses for parents with children and adults in the clinic. Several videos available on the internet show the correct use of these as well (see: 'Links').

The patient experts' recommendations are based on practical experience and offer solutions that can help. Some of the statements are contradictory, which is also evident here. Ultimately, everyone has to make their own experiences and find out for themselves what works.

- Normal eating habits should be maintained or encouraged as far as possible.
- Patients should not switch to tube feeding out of convenience, but only if it is medically necessary.
- A child should have learned to eat properly by the age of 8–10 years at the latest and professional training (e.g. for swallowing) can be used to help meet this goal.
- It is possible to administer medicine only through a feeding tube during the day, and to tube feed in the evening or during the night if the child has not eaten enough during the day.
- Tube feeds may be given at night via a pump, if monitoring is assured. Particular attention must be paid to the aspiration of food into the lungs.
- For some parents, tube feeds seem better than pureed normal food because they are already prepared and balanced, i.e. they contain everything the body needs. This is easier and quicker in everyday life.
- Other parents have a different experience. They feel that food should not be tube food only and it should also contain components of normal food, so that the stool does not become too runny.
- Food supplements and tube feeds are not always tolerated and can easily give the child diarrhoea.
- Please note that medication can also lead to diarrhoea.
- There are different types of tube feeds for children. You should try to identify through experience which one is best for your child. It is important that the feeding tube does not become blocked.
- The tube should be 'rinsed' after every use to prevent it from becoming blocked.
- There are guidelines for taking medication through the feeding tube that must be observed (see chapter: 'Medication'). Again, not all medications can be mixed.
Important note: Some medications cannot be easily administered via a feeding tube (e.g. Procysbi®).
- Important note: As vitamin D in a fluid format sticks to the plastic of the tube, it is not recommended to give this through a tube.
- Care of the stoma should not be 'overdone'.

Diarrhoea

Moderate-to-severe diarrhoea is a common phenomenon in people with cystinosis. Many factors play a role, and it is not easy to deal with in daily life. However, it is just as difficult to find a remedy.

Here's what the guidelines say:

We recommend early diagnosis and treatment of diarrhoea in patients with cystinosis depending on age according to the table.

- The primary goal is to prevent dehydration due to fluid loss and to keep the electrolyte balance stable and prevent other symptoms (e.g. nausea/vomiting, abdominal pain, flatulence).
- At every visit to the outpatient clinic, the problem should be discussed, causes sought and attention paid to failure to thrive, particularly in young children. Weight loss in adults is also a signal to consult a gastroenterologist.
- First of all, the fluid and electrolyte balance should be stabilised for treatment. Finding the cause of diarrhoea is difficult and time-consuming. Medication or tube feeds are the main cause and must be adjusted accordingly. Psychological problems could also play a role.

The group of patient experts is convinced that it is up to each individual patient to find out what is causing the diarrhoea and to look for strategies to deal with it. There are many medications that can cause diarrhoea, especially if they have to be taken in the quantity and composition required for cystinosis. Almost all patients have had or have experience with very thin stools and diarrhoea. Symptoms such as nausea/vomiting, abdominal pain and flatulence are not always associated with diarrhoea but can also be caused by medications.

In the event of severe diarrhoea not improving after 1 or 2 days, it is important to contact the medical team.

There is some practical advice that might be worth a try

- Carrot soup (Moro's soup) helps to regulate bowel movements and diarrhoea. It can always be added to other foods or eaten alone. Recipes can be found online.
- Rice porridge (such as baby rice) or therapeutic foods can be considered.
- The combination of medications should be reassessed.
- Children and adults not in need of tube feeding could try modifying their diet a little.
- If diarrhoea only occurs on weekdays before school or work, there may be a reason that can only be resolved through discussion or psychological support.

Hormones (endocrinology)

A metabolic disease such as nephropathic cystinosis always affects the hormone balance. The effects on the thyroid gland, pancreas, and gonads (testicles and ovaries) are discussed here. Growth hormone is discussed in the chapter 'Bones and muscles'.

Thyroid gland

Thyroid dysfunction can occur in patients with cystinosis. Treatment with cysteamine can delay or even prevent hypothyroidism (underactive thyroid gland).

Here's what the guidelines say:

We recommend at least annual screening of TSH (thyroid stimulating hormone) and fT4 (thyroxine) in patients with nephropathic cystinosis. In the event of abnormal findings, consultation with an endocrinologist is recommended.

After starting treatment with cysteamine, close monitoring over 4 to 12 weeks is initially important in order to adjust the therapy, where required. Under stable hormonal conditions, monitoring should take place every 6 to 12 months.

Patients with cystinosis are evaluated and treated similarly to other individuals with thyroid disorders.

Pancreas

In patients with nephropathic cystinosis, the pancreas may also be affected. Cysteamine therapy does not prevent the development of diabetes in all patients. Diabetes mellitus can occur in rare cases, even before a kidney transplant.

Regular testing is essential to recognise diabetes mellitus at an early stage. Patients who have undergone a transplant are also at risk of developing diabetes due to treatment with cortisone and other immunosuppressants (drugs that prevent rejection).

Here's what the guidelines say:

We recommend determining fasting blood glucose/haemoglobin A1c (HbA1c) at least once a year in patients with nephropathic cystinosis, depending on age and additional risk factors.

***Remark:** In the event of abnormal findings, a joint follow-up examination with an endocrinologist is recommended. For children and adults with cystinosis, the same treatment algorithms and guidelines apply as for all others. Preventive measures for diabetes are carried out as for all people.*

Sex hormones

The sexual development of boys and girls with cystinosis is delayed in comparison to healthy children of the same age, even if they are well treated with cysteamine.

Girls enter puberty with a delay of around 1 to 2 years, which they go through like others. In boys, on the other hand, not only is puberty delayed, but cystinosis also causes men to be infertile. In addition, many male adolescents and young adults have testosterone deficiency.

Fertility in young men

For young male adults who have almost completed puberty, it is possible to have their sperm tested for fertility. This should not be done too late, as the quality of the sperm decreases. If there is a potential desire to have children later on, it is possible to have fertile sperm (mainly

precursor sperm cells) frozen in liquid nitrogen in order to possibly father a child through in vitro fertilisation at a later date.

Here's what the guidelines say:

We recommend offering fertility screening to young men with nephropathic cystinosis as soon as the patient has reached puberty and is willing and able to provide a sperm sample for analysis.

We recommend considering the possibility of cryopreserving sperm or surgically harvesting testicular sperm before starting testosterone replacement. Young men should always be made aware of this option before starting testosterone treatment, as it can also impair sperm production.

Testosterone

There are still no precise studies on the effects of testosterone deficiency in patients with cystinosis. Effects are known from studies with other patients with hypogonadism (hypofunction or decreased function of the testicles). It is likely that men with cystinosis have the same problems. This means that testosterone replacement therapy may improve anaemia and increase bone mineral density. Testosterone replacement can also improve mood and reduce depressive symptoms. In addition, sexual activity, sexual desire, and erectile function are likely to increase.

The expected time to improvement of symptoms following testosterone replacement therapy depends on the duration of pre-existing hypogonadism and the organ system. The pros and cons of testosterone replacement therapy should be considered and discussed with an endocrinologist independently of cystinosis.

Here's what the guidelines say:

We recommend testosterone replacement therapy for hypogonadal postpubertal or adult male patients with nephropathic cystinosis.

Remark: *Hypergonadotropic hypogonadism should be evidenced by low serum testosterone levels on repetitive measurements during morning hours, in the presence of elevated LH serum levels.*

Pregnancy and childbirth

There are now a number of women living with nephropathic cystinosis who have given birth to a healthy child. The problem with this pregnancy is not so much the cystinosis, but the (possibly advanced) kidney disease or previous transplant. Information and guidelines are available from specialist societies and patient organisations for people with kidney disease (see Appendix).

Pregnancy is a risk and always an individual decision for the woman with cystinosis who wishes to have a child. With the potential father she should have the advice of experts in nephrology, gynaecology, paediatrics, and genetics. While we will not go into detail here, it is important to note that a woman who is planning to become pregnant should talk to her nephrologist about all her medications to discuss what may need to be adjusted both before and during pregnancy.

The patient experts recommend that a young woman should have a gynaecological consultation after puberty, regardless of whether she wants to have children. The topic of contraception should also be discussed.

Here's what the guidelines say:

We recommend an overall risk assessment for women with cystinosis and CKD (Chronic Kidney Disease) who are planning a pregnancy.

Remarks:

- *In addition to the factors associated with CKD, Fanconi syndrome, and renal transplantation, these patients need a careful assessment of cardiorespiratory function, thyroid and glycaemic control, and assessment for non-cirrhotic portal hypertension prior to pregnancy. They also require a comprehensive, holistic review in a pre-pregnancy counselling centre.*
- *Care should be based on the current recommendations for CKD patients according to the stage of CKD.*

Cysteamine during pregnancy and breastfeeding

Although there is limited clinical experience of pregnancy in women with cystinosis, the available recommendations for the use of cysteamine are clear. Women should stop taking oral cysteamine as soon as they know they are pregnant and for the entire duration of the pregnancy. However, cysteamine eye drops can continue to be used.

Here's what the guidelines say:

We recommend that women with cystinosis do not take cysteamine during pregnancy.

Remarks:

- *Cysteamine should only be discontinued when pregnancy is confirmed, not before.*
- *Cysteamine eye drops should not be discontinued.*

There are no data on worsening of the disease as a result of discontinuation of systemic cysteamine during pregnancy.

Cysteamine is the specific treatment for cystinosis and has been shown to have beneficial long-term effects on kidney disease and other complications and mortality, but it is recommended that it be stopped during pregnancy because of possible damage to the foetus. Eye drops should not be discontinued as their effect on the whole body appears to be negligible. There is no warning of harm to the foetus from the use of cysteamine eye drops during pregnancy.

After the baby is born, the mother should resume oral cysteamine therapy. This should start with a lower dose and then be increased slowly. The side effects of increasing the dose too quickly are even more common in adults than in children.

A woman with cystinosis who plans to breastfeed her child should be advised that the small amount of cysteamine that may be passed into the breast milk is unlikely to harm the baby.

Here's what the guidelines say:

We recommend resuming cysteamine as soon as possible after labour.

We suggest taking cysteamine at normal doses during breastfeeding.

Neurology

From preschool to school, college, and a profession

Children with cystinosis may have visual-motor and visual-spatial deficits. This means that spatial vision or eye-hand coordination is impaired. This can lead to difficulties in preschool (e.g. when drawing: a stick figure does not have its arms and legs on its body, but next to it), at school (e.g. geometry), or when playing sport (e.g. catching a ball or walking on a straight line). At school, these children sometimes need more time for tests or more time to answer in class.

All of this can reduce their self-esteem. Some young people also find it difficult to make their own decisions (executive functions). Early intervention could reduce the extent of learning difficulties and improve psychosocial difficulties in the long term. Therefore, appropriate tests should ideally be carried out before starting school and regularly thereafter.

Here's what the guidelines say:

We recommend early evaluation for possible cognitive, educational, and psychosocial problems and, if present, timely intervention.

Behavioural, cognitive, and coordination problems as well as balance problems should preferably be treated from the age of 3 by paediatric neurologists with training in developmental neurology or qualified occupational therapists.

We recommend an appointment with an appropriate specialist (such as occupational therapist or psychosocial specialist) as a preventive measure as early as appropriate and if

fine motor, visual motor or visual spatial deficits are identified, then intervention should be recommended to reduce those deficits and to provide education and training for parents.

Preschool and school

Good co-operation with kindergarten/pre-school and school is important. In individual cases, it has been shown that better performance at school can be achieved by changing the learning conditions and the setting of tests.

The patient experts have compiled a comprehensive list of recommendations for the start of a new phase of life. It is recommended to order relevant information material for educators and teachers from the national patient organisations or download it from their website.

Here are some key topics that should be addressed with the new kindergarten, preschool, or school before starting. The child or adolescent should be involved in this discussion in an age-appropriate way.

- Children with cystinosis are often underestimated in what they can do due to their smaller size.
- They can attend kindergarten/pre-school and school according to their age.
- Free access to fluids and always being allowed to go to the toilet (even during lessons) is vital.
- Toilet training is a topic to talk about in kindergarten.
- Eating habits/feeding tube and medication are issues.
- Any limitations that the child may have should be mentioned but not overemphasised, e.g. spatial vision (e.g. when painting) and physical weakness (can the child open all doors in the building?).
- With older children, the smell of cysteamine could also be an issue.
- People living with cystinosis are very sensitive to light. Some children might need sunglasses in the classroom on winter days because the electric light is too bright.
- Who talks to classmates?
- Who informs the other teachers?
- What kind of bullying strategy is in place at school?
- Is there any need or desire for an information event about cystinosis for parents and pupils?
- After the first few weeks, a meeting should be arranged with the class teacher to address any problems. Is a discussion about compensation for disadvantages necessary (e.g. longer time for class work, less homework)?
- In some countries, there is special support for students with disabilities or medical needs.
- At some stages, home schooling or lessons via official internet platforms could perhaps also be considered. However, this is only recommended for absolute exceptions.
- Important note: Who can be contacted in the event of an emergency at nursery or school? What is an emergency?
- Socio-educational or socio-psychological support should be sought if overwhelming difficulties arise.

Apprenticeship/training on the job

For adolescents with cystinosis about to start apprenticeship or studies, young adults have given some advice.

- People with cystinosis can take up any profession they wish. Everyone can decide for themselves what they feel comfortable with, depending on their aptitude, strength, and resilience.
- There is hardly any occupational group in which people with cystinosis do not already work or have been working.

Applying for an apprenticeship or a job:

- All potential topics of discussion should be reviewed with a trusted person prior to an important interview.
- A counselling session with an employment agency/career consultant can be helpful.
- Disclosing a chronic illness during an interview is not mandatory, but it should be considered if the interview is successful, or an employment contract needs to be signed.
- Internships, voluntary work, special additional training, and similar experiences should be included in the CV, along with any relevant confirmations or letters of recommendation.
- The advantages of hiring a person with medical needs should be highlighted, such as the possibility in Germany for the labour office to cover part of the salary under certain conditions.
- The employer's policy regarding absences for medical appointments should be clarified, including whether flexibility is offered, whether missed hours must be made up at a later time, and, if so, under what conditions. Additionally, it is important to determine whether an official disability status influences the applicable policy.

Applying for university

In principle, this is no difference to people without a chronic illness.

- Application documents should be read carefully and filled out accurately.
- For any questions, it is advisable to seek guidance from the university support services.
- All supporting documents should be included (such as a medical certificate, if required).

Once you are accepted as a student:

- Contacting the disability support services at the university may be helpful, as they can offer accommodations such as flexibility with exam dates in case of illness or extended time for exams if writing quickly or for long periods is difficult.
- Completing exams on a computer may also be an option.

Further neurologic symptoms

It is known that some people with cystinosis can show damage to the brain tissue (cerebral atrophy) and calcifications in the brain. However, these changes do not necessarily show themselves in clinical findings and symptoms.

Symptoms may include unexplained headaches, dizziness, swelling of the optic nerve and increased intracranial pressure. A magnetic imaging resonance (MRI) scan can be performed to diagnose these symptoms, but is not recommended as a preventative measure in the absence of clinical symptoms.

Here's what the guidelines say:

We do not recommend an early MRI in patients with cystinosis in the absence of clinical neurological symptoms.

We do recommend early sensorimotor testing as there are interventions available that can help the child with learning and socialising if problems are identified.

Idiopathic intracranial hypertension (pseudotumor cerebri)

Idiopathic intracranial hypertension (formerly called pseudotumor cerebri) may occur in some patients. This comes with a relatively high accumulation of fluid in the brain that presses on the optic nerve and other areas. Severe headaches and a swollen optic nerve can be signs of this. The disorder is not always recognised in a cranial MRI (cMRI) scan, so further examinations by an ophthalmologist (specialised eye doctor) and lumbar puncture to measure intracranial pressure are often necessary. Sometimes idiopathic intracranial hypertension is first diagnosed by them because they see the swollen optic nerve in a regular exam. It is not fully understood where this comes from, but it certainly has to be treated accordingly.

Eyes

Cystinosis leads to the formation of crystals on the surface of the eye (cornea). The crystals can be detected with a slit lamp examination by an ophthalmologist. However, the first crystals do not form immediately after birth, but are often only detectable after the first year of life or later. Crystals on the surface of the eye lead to high sensitivity to light (photophobia).

Here's what the guidelines say:

We recommend patients with cystinosis be treated with a combination of systemic cysteamine and cysteamine eye drops.

Remarks:

- *We do not recommend favouring one formulation of cysteamine eye drops over another. The formulation should be selected based on availability and tolerability by the patient.*

- *Recommended topical treatment frequency depends on the respective pharmaceutical formulation.*

As the cornea has no blood vessels, cysteamine taken by mouth and circulated in the blood system cannot reach the cornea. Therefore, to reduce crystals on the surface of the eye, topical cysteamine, in the form of eye drops or eye gel, must be used.

There is no universal answer to the question of when to start cysteamine eye drops. Initiation of topical therapy can be delayed until the family has become accustomed to the many demands of the systemic treatment routine. The optimal time to start cysteamine therapy for the eyes is different for each patient and should always be determined in consultation with the treating eye specialist.

Later, there may be further damage to the eye that cannot be treated with eye drops. Damage to the retina and the posterior layers of the eye can only be prevented by taking oral systemic cysteamine continuously (capsule or liquid form) from an early stage.

In adults diagnosed with the ocular form of cystinosis which only affects the eyes, treatment with cysteamine eye drops should begin immediately.

There are different variants of the eye drops, but no differences in effectiveness have been found. This means that, in general, all cysteamine eye drops are equally effective when used correctly.

These formats of eye drops are available:

- Liquid form (trade name in 2024: Cystaran®): These eye drops must be applied every hour if possible (except at bedtime).
- Gel-like form (trade name in 2024: Cystadrops®): These drops adhere better to the cornea, therefore they only need to be taken 4–6 times per day.

Both products contain benzalkonium chloride as a preservative, which can lead to side effects in some cases.

- In some countries, pharmacies produce cysteamine eye drops (from mercaptamine chloride). These drops must be applied every hour if possible (except at bedtime) or at least 10 times per day. Pharmacies specialised in the production of these drops can be found via recommendation from clinics or patient organisations.

Cystaran® and Cystadrops® are not available in all countries, so patients may not have the option of deciding which to choose. In some countries, only eye drops produced in pharmacies are available.

The tolerability of eye drops is different for each patient. Some patients prefer the more liquid form of the eye drops, others the more viscous form. If a burning sensation occurs when administering eye drops, the cause should always be clarified with the ophthalmologist. In

many cases, the cystine crystals on the cornea in conjunction with the eye drops cause severe itching and burning. This improves when the crystals are reduced. To reduce the burning, guidelines suggest applying 1 or 2 eye drops for dry eyes several minutes before administering the cysteamine eye drops. Only a few people actually develop an allergy to cysteamine or the additives in the eye drops.

The liquid form of the eye drops is best used every waking hour, although for some patients this can be an almost impossible task in everyday life. Some doctors recommend using eye drops several times in succession at intervals of around 15 to 20 minutes in the morning or evening. The use of these eye drops can then be forgotten about for a few hours. Using eye drops too frequently is not considered to be harmful.

It can be a challenge to administer cysteamine eye drops to small children. It is important to start slowly and approach the task with as little conflict as possible. One dose per day without any stress or struggle should be the first goal. Once this goal has been achieved, it then makes sense to slowly increase the number of doses to the individual target dose.

One recommended way of administering eye drops without stress at the start of treatment is for the child to lie on their back as relaxed as possible, ask them to close their eyes, and then drop the eye drops onto the closed eye close to the nose. The eye is then gently opened by pulling down the lower eyelid (See more tips at the end of the chapter).

For adolescents and adults, it is good to know that hard contact lenses can be worn when using cysteamine eye drops. A precise fitting by an optician and possibly trying out different products is necessary. Soft contact lenses have to be taken off before applying cysteamine eye drops because these lenses react with benzalkonium chloride. Soft lenses can be put back into the eyes 15 minutes after applying the drops (see individual product leaflets for more information).

In addition to the formation of crystals, patients with cystinosis may, in rare cases, experience other eye-related complications. Increased intracranial pressure (idiopathic intracranial hypertension, also known as pseudotumor cerebri) causes chronic headaches and visual disturbances such as blurred vision, double vision, and visual field restrictions. Damage to the optic nerve can lead to anything from slight restrictions in visual sharpness and in the visual field to complete restriction of the visual field or even blindness. If patients with cystinosis experience the symptoms described above, they should seek medical help by a specialised ophthalmologist immediately (see also 'Neurology').

In addition to examination of the eyes using a slit lamp, the guidelines also recommend the use of imaging procedures depending on availability. Once the administration of eye drops has been successfully established on a permanent basis and there are no unusual symptoms, the eyes should be examined by a specialist at least once per year.

Some practical advice from patient experts

- It is important to wear sunglasses, a sun hat, or a cap to protect the eyes on sunny days. A wide brim on a hat or cap is sufficient for children.
- Some children cannot tolerate electric lights in the morning. A dimmer connected to the light in the room can help. Some children might even need sunglasses in the classroom on winter days because the electric light appears too bright.
- Always apply eye drops at fixed times to avoid them being forgotten.
- To integrate eye drops into the daily routine, you can combine the administration with certain activities, e.g. brushing your teeth (once before and once after).
- To help avoid the burning sensation, use ordinary (saline) eye drops for dry eyes before or 10 minutes after applying cysteamine eye drops.
- Eye drops made by a local pharmacist should be used according to the pharmacy during the day (cool or at room-temperature); industry-made eye drops, which contain preservatives, are recommended for longer journeys or when travelling.
- For adults, special sunglasses with the darkest possible rim filter are recommended. Caution: The colour should not be darker than is permitted when driving a vehicle.

These tips may help when administering eye drops

- Children may blink and rub their eyes after treatment. It may be better to let them do that until they get used to the drops and then slowly try to distract them from doing this (such as immediately starting to play with them, so they have to use their hands for something else).
- If the child gets hold of a toy or even a mobile phone, they are less likely to struggle with their hands and will not wipe away the eye drops immediately. Use of a mobile phone may provide the bonus of allowing the child to look at something briefly (e.g. photos or a video), keeping their eyes open for treatment.
- As children get older, it can be explained to them that it is better not to blink straight away or rub their eyes after the eye drops have been used. Some parents have shown their children videos of administering eye drops which can help them to understand the process.
- The child should be taught to administer the eye drops themselves as soon as possible. However, the age at which a child is ready and willing to do this will vary. Even if it does not really work from the first few days, let them try alone as this will increase their independence and the whole process may start to feel less invasive.

Bones and muscles

Cystinosis metabolic bone disease (CMBD)

Cystinosis can cause problems with bones and muscles. One common symptom prior to diagnosis in children aged 6 months and upwards is rickets due to the loss of phosphorous and bicarbonate from the kidneys (Fanconi syndrome). Children can present with bone pain and be slow to crawl or walk. Growth might not be as expected for their age, and more frequent

bone fractures, pain in the legs, ankles, knees, or feet, along with flat feet, knock-knees, or scoliosis can also occur.

In adolescents or adults, problems with the muscles in the throat can affect swallowing, sometimes speech, and even breathing in severe cases. Muscle wasting and bone issues are typically first noticed in the hands. For example, some individuals can find it difficult to open water bottles and jars. Consistent support and training exercises from the physiotherapy and/or occupational therapy teams can help with this.

Bone problems can be prevented or slowed down by treatment with various nutritional supplements. The right combination of electrolytes, particularly phosphate and calcium, is important here. A well-adjusted supply of vitamin D, and possibly carnitine, will also support bone and muscle development and prevent rickets.

Here's what the guidelines say:

We recommend age-appropriate treatment of metabolic bone disease in cystinosis, including correction of mineral metabolism, optimisation of physical activity and/or physiotherapy, orthopaedic treatment and growth hormone treatment if indicated.

Remarks:

- *Therapeutic decisions should be made on the basis of disease progression and not on the basis of a single laboratory value, taking into account all available CMBD assessments.*
- *Initiate interventions aiming to prevent/decrease bone pain, leg deformities, and muscular weakness. Include daily physical activity, the use of physiotherapy and occupational therapy, if indicated.*

Growth hormone

- The use of recombinant growth hormone (rhGH) therapy may be appropriate for children with nephropathic cystinosis who experience persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile. This should be considered if other treatable causes of growth failure, such as malnutrition, acidosis, and hypothyroidism, have been addressed and the child still has growth potential.
- rhGH therapy may also be considered one year after kidney transplantation in children with persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile. This is particularly relevant if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not feasible.

Orthopaedic involvement

- Initiate stage-appropriate therapy for children with flat feet, including sensorimotor insoles and, if necessary, surgery, as long as the deformity is flexible.
- Perform guided growth techniques at least 2–3 years before skeletal maturity (epiphyseal closure).
- Initiate stage-appropriate therapy for scoliosis, including physiotherapy, brace, and surgery, if necessary.

In order to monitor bone and muscle health and depending on the type of health service in the country, the following specialities should be accessed: an experienced orthopaedic specialist, a metabolic outpatient clinic, and a nutrition specialist or dietician at regular intervals for assessment and advice. Blood levels of electrolytes, vitamin D, and phosphate, and possibly also carnitine, should be checked regularly so that treatment can be adjusted, where necessary. Diet also has a major influence on electrolytes. Adjusting the diet or modifying the intake schedule may allow for a reduction in medication dosage.

For patients, physical activity is an important factor that can be modified to reduce bone and muscle problems. Physiotherapy, and later occupational therapy, is recommended in order to learn exercises that prevent muscle atrophy and its associated problems.

Here's what the guidelines say:

We do not suggest physiotherapy for prevention prior to any muscular or motor developmental delay.

We suggest early physiotherapy in the presence of muscular weakness or motor development delay.

Remarks:

- *We recommend that all patients are informed about their current muscle status.*
- *All patients, even the youngest, should be encouraged to participate actively in physical exercise.*

Orthopaedic involvement

Children should be actively encouraged to engage in all normal childhood physical activities where they will have the opportunity to use their muscles on a regular basis. There are no restrictions on what a child with cystinosis can do physically, unless they are told otherwise by their doctor. Foot deformities and knock-knees are very common and occur in most children, even if they undertake regular physical activity.

Hands

Muscle atrophy and bone deformities in the hands are particularly common in adults, and less frequently in children. Some of those affected have difficulty writing by hand and/or can no longer open water bottles. The muscles atrophy and the hands slowly stiffen if they are not used regularly. Consistent training can help with this. Exercises can be learnt with support from physiotherapy or occupational therapy – the therapists should ideally have an additional qualification in ‘hand rehabilitation’ or ‘hand therapy’.

Feet

Early consultation with an orthopedic specialist is important, even if young children are not at the point of needing insoles or orthotics. For children with very unstable or flat feet, sensorimotor insoles can offer excellent support and stability. If physiotherapy is recommended, it can be beneficial to practice the exercises together at home to reinforce progress and build strength. Insoles and orthotics can also be highly beneficial for adults. Regular assessments and a tailored approach can help ensure that the right solutions are implemented for both children and adults.

Legs

Insoles can help to relieve pain in the knees and legs in children and adults. If knock-knees are severe in children, a guided growth technique may be recommended by an orthopaedic specialist. This common method involves placing a plate (8-plate) over the growth plate on the inner side of the knee(s) in a minor operation. As the child grows, the plate helps straighten the knee and in most patients the plate can be removed at a later date. This approach can be very effective at correcting knock-knees, but success requires its use before growth is complete and the growth plates have closed.

Scoliosis

Some adolescents with cystinosis (around 30–50%) develop a slight curvature in the back, possibly due to poor muscle development along with weak connective tissue. Scoliosis is a painful condition which requires targeted physiotherapy. Exercises must also be done at home to prevent worsening. Further treatment is often not necessary.

To prevent further curvature, some children and adolescents may have to wear a corset. The effect is similar to that of a brace. The deformity is largely straightened by applying pressure and tension. In most cases, this therapeutic approach avoids the need for an operation to straighten the spine.

This is what affected patients report

- A corset is very uncomfortable, especially at the beginning. Movement is more or less restricted, but the patient will eventually get used to it.

- T-shirts, tops, or waistcoats can be worn underneath a corset to reduce discomfort and prevent pinching. Care should be taken to ensure there are no fabric folds under the corset when dressing. Trousers with a wide waistband are recommended for added comfort.
- How long the corset needs to be worn each day varies from patient to patient. For some, 12 hours a day will be sufficient, while others also wear it at night. The corset is taken off during sport or physiotherapy.
- Physiotherapy is an important addition to the management of scoliosis.
- It is easy to see who is wearing a corset, but it is not always easy for young people to put up with silly comments about it from others.
- As spinal surgery is the only alternative to wearing a corset, young people typically endeavour to wear their corset consistently.

Which sport is the right one?

Many children and adolescents enjoy doing sport. The easiest way to encourage regular activity is to take children hiking, let them ride pedal scooters and bicycles from an early age, climb trees and climbing frames, and run and jump. There is no reason to be particularly careful with children with cystinosis – they can do all kinds of sports as long as they feel comfortable. It is a good idea to initially introduce children with cystinosis to sports where there is no pressure to perform and where training levels can be easily measured.

Regular exercise is also very important for adult patients with cystinosis, although it can be difficult for patients with cystinosis to find a sport that they enjoy. Some individuals enjoy group activities because it motivates them to keep up with others, while others have had bad experiences in sports clubs because they do not feel welcome due to their low fitness levels.

For this reason, it is more important for patients with cystinosis to be physically active in the first place than to look for the best sport to improve muscle function. Only those individuals who enjoy an activity will do it regularly and continue this over a long period of time.

Tips from the patient experts

- Parent-child gymnastics classes are a good place to start.
- Sports club/groups which are attended by other children from kindergarten/school will motivate attendance and support regular activity.
- Ballet, dancing, route climbing/bouldering, fencing, martial arts, football, horse riding, tennis, badminton, hiking, swimming, cycling, and skiing are all sports that are practised and recommended by patients with cystinosis. The list can be expanded at any time according to patients' preferences.
- Children and young people who tire rapidly could also try a sports group for disabled and non-disabled children.
- Regular fitness training with equipment (three times per week) can lead to good muscle strength.
- Rehabilitation sports classes are a good alternative for adults with cystinosis who do not feel really fit or athletic.

- Here is a personal statement from a patient: "When it comes to swimming and team sports, it is important to look for clubs where there is no pressure to perform. I qualified as a lifeguard and now give swimming lessons to children. I played floorball at a team, which doesn't take part in any leagues, and the players were aged between 14 and 70."
- In addition to sports, other activities and hobbies might help to support hand strength and dexterity – examples include playing a musical instrument, crafts (e.g. knitting, painting, clay modelling, baking), and even playing video games.

School sports

Experiences with school sports vary greatly. In any case, it is good to stay in communication with the teachers and point out the problems with cystinosis (regular drinking and toilet breaks required, lack of energy and extreme tiredness in child). If the demands of school sports are too high, a grade exemption is one way to ensure physical activity in school sports without the pressure of grades.

Transition

In recent years we have learnt that transition from paediatric medical care to adult care is extremely important for the future of young adults living with cystinosis. In some countries, hospitals have set up long-term transition programmes (from the age of 12) to guide these patients towards becoming independent and responsible individuals who are able to discuss their health issues with doctors and know how to integrate health needs (ordering prescriptions, making hospital appointments) into their daily life.

In parallel to this programme, parents also need to be supported to adjust to the new situation. Responsibility for patient care must be transferred in a stepwise manner to the young adult.

Here's what the guidelines say:

We recommend building transition programs for adolescents with rare multi-organ diseases such as cystinosis.

In particular, workshops, joint visits, extended or multidisciplinary appointments, promotion of health literacy, appointment arrangement services, screening for psychological stress and abnormalities as well as the use of technical elements (websites, apps, texting) have shown beneficial effect.

Special attention must be paid to the psychosocial wellbeing of the young adult. The desire to build a life of their own and deal with a chronic disease is a challenge, which is often overwhelming. Non-adherence to treatment and depressed feelings can occur in some individuals.

Here's what the guidelines say:

We recommend establishing a psychosocial needs assessment and needs-based psychosocial support for cystinosis patients, independent of age, and (in children with cystinosis) for their caregivers and siblings to enhance the care situation, participation, and mental health of affected patients and families.

There is still more robust advice that the patient expert group has to give for families and adolescents.

Of course, it would be best if there was no need for a harsh transition for adolescents from the paediatric clinic to one for adults. This would require a multidisciplinary team that also includes doctors for adults. Unfortunately, this is not possible at most clinics. In the worst-case scenario, the patients in the new clinic have to educate the doctors about their illness and even share their own knowledge.

It is good to involve children and adolescents in clinic discussions at an early stage, letting them ask their questions independently and have them answer questions from the practitioners. This may not always work immediately, but parents should only intervene carefully if they realise that the conversation is going in the wrong direction. Good doctors usually notice this and redirect the conversation.

To prepare for the actual transition, it can help to compile the medical history of the patient, via input from the caregiver and adolescent. We recommend creating a folder with all the names and phone numbers of practitioners, pharmacies, and non-clinical therapists, for easy reference.

The following advice comes from parents and young adult patient experts. It may not meet everyone's experiences, but it is a good start to think about transition:

- Even young children should always be taken to the doctor's appointment. They will not always understand everything, but they will learn to ask questions themselves by imitating their parents.
- Parents can explain difficult topics to children after the consultation if the doctors do not do this themselves.
- From the age of around 12 years, young people can have the conversation with the doctor themselves. The parents should be present, but they should listen and ask their own questions later.
- From this age, parents can also plan future visits to the doctor together with their child, i.e. consider what needs to be taken along, which medication requires a prescription, and what questions have arisen since the last visit.
- If there is medical 'homework' (e.g. writing down how much fluid intake each day), young teenagers can also do this on their own.
- Important note: Adolescents and even children can ask about their medication during the consultation. Some individuals may want to switch from liquid medication to tablets or change certain set treatment times – a certain amount of say should always be allowed. However, this should not mean that everything is always possible!

- Medication can be prepared together and, eventually, young individuals will be able to do this on their own. A good motivation is that only those who know what medication to take and at what time can travel without their parents.
- Young people can also order refills of the medication themselves if they so wish.
- Important note: A child or a young person who does not yet feel able to fulfil these tasks should not have to do something just because their parents do not have the time any more. In this case, other ways to manage this effectively have to be found.
- Many young people travel alone for the first time when they are still at school, for example to a youth camp or to visit relatives. These are good opportunities for them to prove to themselves (and their parents) that they can cope on their own in a safe place. Medication can be taken along already prepared for use each day and if a dose is missed, no serious harm will be caused. Experience shows that young people tend to remember their medication better away from home than at home.
- Children and adolescents who know that their parents trust them even if something goes wrong become independent more quickly and have better self-confidence.
- Before the actual transition to the adult clinic, the pediatric team should be asked for recommendations for a new clinic. Any easier ways to share information between care teams is always desirable.
- For those first few visits to the new clinic, parents should accompany the patient. Gradually, young adults will be able to look after themselves. However, this does not preclude the need for parents to be involved in special situations (start of dialysis, transplantation, etc).
- If co-operation with new doctors is difficult or does not seem possible, it may be helpful to have a discussion moderated by a member of the social services team.
- Young adults or their parents should seek psychological or psychosocial help if this period of transition becomes too difficult for them.

Integrated care

Nephropathic cystinosis is a very rare and complex multi-organ disease. This means that an increasing number of different organs are affected as the disease progresses, presenting treating physicians with a variety of diagnostic and therapeutic challenges. After diagnosis in childhood, most patients are initially treated by a paediatric nephrologist, as the kidneys are the first organ to be affected. For adult patients too, a nephrologist will typically be responsible for the entire treatment.

The respective clinical expert for other affected organs must be included in the treatment pathway. Due to the rarity and complexity of the disease, the organs that are affected in addition to the kidneys are not always known to treating nephrologists and may not be adequately taken into account during diagnosis and treatment. Since treatment with cysteamine has only been available since the 1980s, patients in the 2020s belong to the first adult generation. This means that there is still a lack of empirical (research-based) knowledge, particularly for the treatment of adult patients.

Patient experts know that integrated care within a centre specialised for cystinosis makes it easier for patients to organise their visits. In addition, the exchange of expert knowledge for

this disease, whose long-term course remains unclear, and immediate consultation within the multidisciplinary team is important. The transfer of expertise is urgently needed for long-term healthcare.

In addition to multidisciplinary clinical care, other factors must be taken into account:

- Age-specific aspects
 - In the case of children, for example, parents or carers must be involved as responsible individuals.
 - The organisation of healthcare differs between children and adults.
- Adolescence is considered to be a difficult phase for patients with cystinosis, for example, in terms of acceptance of and adherence to therapy.
- Patients with juvenile cystinosis must be examined by experts according to their clinical symptoms.
- Psychological factors play a particularly important role during and after the transition of young people from paediatric to adult care.
- As an excessive number of follow-up visits can become a burden, several appointments with different specialists should be arranged on the same day, where possible.
- A case manager for patients can provide an increased level of assistance and support, particularly when transitioning from paediatric to adult services.

The guidelines list the specialists and special examinations that are important for patients with cystinosis during the course of their disease as follows. Depending on the clinic routines in different countries the number of visits may differ. Therefore, the numbers in brackets are suggestions from the patient expert group.

On diagnosis (Infantile nephropathic cystinosis is usually diagnosed at 6–24 months of age)

Paediatric nephrology with accompanying nutritional advice
Eye care (from 24 months of age)
Speech therapy for eating disorders
Psychosocial support for the family, as needed

Infant (from 24 months–6 years)

Paediatric nephrology (every 2–3 months) with accompanying nutritional advice
Endocrinology (in case of abnormalities in growth and/or thyroid parameters as required, otherwise once per year)
Dietician (at least once per year)
Neurology (examination at pre-school age, then once per year as required)
Speech therapy (at least once per year)
Physiotherapy (at least once per year)

Orthopaedics (at least once per year)
Occupational therapy (at least once per year)
Eye care (once per year)
Psychosocial support for the family, as needed

Children and teenagers (6–14 years)

Paediatric nephrology (every 2–3 months depending on kidney function) with accompanying nutritional advice
Endocrinology (in case of abnormalities in growth and/or thyroid parameters as required, otherwise once per year)
Neurology (at least once per year)
Speech therapy in case of voice disorder, as required (at least once per year)
Physiotherapy (at least once per year)
Orthopaedics (at least once per year)
Occupational therapy (at least once per year)
Eye care (once per year)
Pneumology (once per year)
Ultrasonography of upper abdomen (once per year)
Psychosocial support for family and patient, as needed

Adolescents (aged 14 years and older) and adult patients

Paediatric nephrology (every 2–3 months depending on kidney function) with accompanying nutritional advice
Endocrinology (in the event of abnormalities in growth and/or thyroid parameters, endocrine/exocrine pancreatic function, hypogonadotropic hypogonadism as required, otherwise once per year)
Clarification of fertility in boys and sperm storage if necessary, with monitoring as required
Neurology (at least once per year)
Speech therapy in case of voice disorder, as required (at least once per year)
Physiotherapy (at least once per year)
Orthopaedics (at least once per year)
Occupational therapy (at least once per year)
Eye care (once per year)
Pneumology (once per year)
Cardiology and vascular medicine (once per year)
Ultrasonography of upper abdomen (once per year)
Gynaecology (provide education about pregnancy and contraception)
Psychosocial support for the family and the patient, as needed

Coordination of the transition between the paediatric clinic and the clinic for adults.

It might be helpful involving a local pharmacy or a pharmacist at the clinic in the treatment pathway.

Appendix

Conflict of Interest Management

All authors of this patient version also participated in the development of the medical S3-Guideline Cystinosis. All members of the guideline group disclosed their potential conflicts of interest in accordance with the Institute for Medical Knowledge Management (AWMF). These conflicts were evaluated by a board and categorised as none, low, moderate, or high. A transparent procedure for managing these conflicts was implemented to ensure the independence and integrity of the guideline. A low conflict of interest resulted in the limitation of leadership roles or the appointment of a co-coordinator without conflicts. A moderate conflict of interest led to abstention from voting on the affected topic and exclusion from leadership roles. A high conflict of interest resulted in exclusion from discussions and voting. Further details on the conflicts of interest, as well as the conflicts of interest themselves, can be found in the associated guideline report (See: S3-Leitlinie Cystinose, AWMF-Register Nr. 166/006, <https://register.awmf.org/de/leitlinien/detail/166-006>).

Medication survey

How to use this table? Take the folding box or leaflet of your medicine and look for the active ingredient mentioned. Now you can search for the drug in the table below to find out more about it. The table is not exhaustive and does not replace the mandatory advice of a doctor or pharmacist – it is simply intended to provide practical information.

Medication	Purpose	To note	Storage
Amlodipine	Expands the blood vessels and improves blood circulation. Treats high blood pressure	Avoid combination with pineapple, bitter orange, pomelo	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Atorvastatin	Lowers the cholesterol level	Avoid combination with pineapple, bitter orange and pomelo If you experience muscle pain or bloody urine, please inform your doctor immediately This can be taken in the morning	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Belatacept	Prevents the rejection of organ transplants	There are some interactions between belatacept and other medicines	Unopened vials: between 2° and 8°C (36°F and 44°F)

		To avoid problems, have your medication checked by a doctor or pharmacist	(refrigerator) – do not freeze!
Bisoprolol	Treats high blood pressure and reduces the pulse	Avoid the combination of bisoprolol and sultanol/salbutamol/albuterol (asthma therapy) Ask your doctor or pharmacist whether the combination is necessary	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Calcium salts • gluconate • carbonate • lactate • oxide	Treats calcium deficiency	There should be an interval between taking calcium and phosphate: • Liquid calcium and liquid phosphate: 30 min • Liquid calcium and solid phosphate (capsules or tablets): calcium first, phosphate 30 min later • Liquid phosphate and solid calcium (capsules or tablets): phosphate first, calcium 30 min later • Solid calcium and solid phosphate: 2 hours in between Calcium salts can be mixed with magnesium, sodium, and potassium salts if required (not with phosphate). Calcium oxide is very low absorbing – please ask your doctor about switching to another compound (lactate or gluconate)	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F) Shelf life of calcium salts after dissolving them in water: 24 hours
Candesartan	Dilates the blood vessels and improves circulation. Treats high blood pressure	Do not combine with ibuprofen, naproxen, or diclofenac without consulting your doctor or pharmacist	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)

(Levo-) Carnitine	Treats carnitine deficiency	Administer the solution in equal doses throughout the day to avoid gastrointestinal problems. Dilution in water or juice is possible	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Chlorophyll	To reduce body odour	Pigment from green leaves. No evident data available, but may help with cysteamine odour Ask your doctor or pharmacist (liver condition) before taking it	
Clonidine	Treats high blood pressure	Avoid stopping oral intake to avoid fluctuations in blood pressure. Patients who wear contact lenses should use hyaluronic acid to moisten their eyes	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Corticosteroids • Prednisone • Prednisolone	Prevents the rejection of organ transplants	Corticosteroids have an activating effect, so take them in the morning if possible. Please never stop taking them abruptly or without authorisation to avoid rejection of the graft Corticosteroids increase the breakdown of vitamin D, ask your doctor for a status determination	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Cyclosporine	Prevents the rejection of organ transplants	Avoid combination with pineapple, bitter orange, pomelo, or alcohol. There are different dosage forms (capsules vs tablets vs oral suspension; immediate release vs prolonged release) – these formats are not interchangeable. To avoid administration errors, please check the medication schedule or ask your doctor or pharmacist for advice.	

		Cyclosporine should be taken on an empty stomach with water. Do not change the method of administration to avoid fluctuations in blood levels. Please report any side effects to your doctor. Side effects may include diarrhoea, urinary tract infections, tremors, high blood pressure, headache, insomnia, and fever. There are some interactions between cyclosporine and other medications – to avoid problems, seek advice from your doctor or pharmacist. Avoid sunlight and wear UV protection	
Cysteamine itartrate (oral) Cystagon® Procysbi®	Depletes cystine in the body	Avoid combination with pineapple, bitter orange, and pomelo Cystagon® capsules: Eat something before intake with a large glass of water, milk, or juice. Administration every 6 hours 'Shots' or refilled capsules are possible – specialised pharmacists can help in cooperation with doctors Procysbi® capsules: If possible do not eat 1 hour before or 1 hour after taking Procysbi®. Take with apple juice or orange juice (no milk) 'Shots' are possible – pharmacists can help in cooperation with doctors	Cystagon® capsules: Dark and dry (wardrobe or cupboard) Dry powder: Dark and dry (wardrobe or cupboard) Cystagon®-water mixtures should be administered rapidly Cystagon®-water mixtures can be frozen for 6 hours, but shake after thawing. Fresh production is preferable (empirical values, no stability data available) Procysbi® capsules: Cold, store in the refrigerator

			Procysbi® shots: Cold , store in the refrigerator
Cysteamine bitartrate (eye drops)	Removes cystine from cornea	Infants or small children: If eye drops are not accepted because of the dropping procedure – put the drops into the angle between eye and nose while the eye is closed. If the child opens the eyes, the drop will go into the eye. 10 min after applying drops, wipe the closed eyes with a damp cotton pad to avoid odour. If the eyes are burning, hyaluronic acid can be used 3–4 min before and 10 min after applying the cysteamine eye drops. Eye drops <u>without</u> preservatives are possible – pharmacists can help in cooperation with doctors	Eye drops <u>with</u> preservatives: Dark and dry (wardrobe or cupboard). Eye drops <u>without</u> preservatives: Freeze until use Ask your pharmacy how to keep or transport an open bottle.
Cholecalciferol and other vitamin D compounds	Treats vitamin D deficiency	Take after a meal. Daily intake is better than weekly intake. Do not give fluid vitamin D through a feeding tube as it sticks to the plastic	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Erythropoietin - Epoetin • alpha • beta	Helps blood formation (red blood cells)	Take care of iron status (i.e. ferritin, transferrin). Read the medical instructions or ask your doctor or pharmacist for advice on use	Unopened vials: Between 2° and 8°C (36°F and 44°F) (refrigerator) – do not freeze!
Famotidine	Reduces stomach acid production	Less effective than omeprazole or pantoprazole. Ask your doctor or pharmacist about short term treatment with proton-pump inhibitors	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Hydrochlorothiazide (HCT)	Treats high blood pressure, helps with acid excretion	Check electrolytes 2–4 weeks after initiation of HCT therapy Do not combine with ibuprofen, naproxen, or diclofenac without consulting	

		your doctor or pharmacist. HCT can influence some medical tests (e.g. hormone assays, corticosteroid tests). Please tell your medical specialist that you are using HCT Please report all side effects which occur after initiating or increasing dose of HCT to your doctor. Side effects can include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, muscle pains, or cramps (list not complete). Check your vitamin B₁ status during long-term treatment. Limit sunlight and wear UV protection	
Iron salts • sulphate • fumarate • glycinate	Treats iron deficiency	Combination with vitamin C (fruits, vegetables) increases absorption. Evening intake can avoid stomach-gut-problems (obstipation)	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Laxatives • Macrogol • Bisacodyl	Treats obstipation	Laxatives are problematic because they affect the electrolyte balance. Please ask your doctor or pharmacist about alternatives such as • Magnesium citrate • Lactulose • Psyllium husks (each should be checked individually) If laxatives are necessary, check electrolyte status on a regular basis	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Lercanidipine	Expands the blood vessels and improves blood circulation. Treats	See Amlodipine	

	high blood pressure		
Levothyroxine	Replaces thyroid hormones	The first pill of the day! Please take with water only, early in the morning. Wait 20 min before cysteamine or other medicines. Wait another 30 min before eating. Please do not split tablets because the resulting tablet halves do not contain the active ingredient in equal parts – please ask your doctor or pharmacist for a suitable dosage	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Magnesium salts • citrate • glycinate • oxide	Treats magnesium deficiency	Magnesium citrate: To avoid diarrhoea, dilute in water or juice and take step by step over the day Magnesium oxide has a very low absorption – please ask your doctor for a change to another compound (-citrate or -glycinate) Magnesium salts can be mixed with calcium, sodium, and potassium salts to be drunk over the day, if necessary (not phosphate)	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F). Shelf life of calcium salts after dissolving in water: 24 hours
Metoprolol	Treats high blood pressure, calms the pulse	See Bisoprolol	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Moxonidine	Treats high blood pressure	See Clonidine	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)

Mycophenolate (MPA)	Prevents the rejection of organ transplants	There are different forms (capsules vs tablets vs oral suspension; immediate release vs extended release) – these forms are not interchangeable. Sometimes you will have different forms at the same time – please check the medication plan or ask your doctor or pharmacist to avoid administration errors MPA (CellCept®) is subject to the enterohepatic circulation – a recycling system in the intestine that absorbs some of the MPA from the gut. If you have diarrhoea for more than 24 h, please inform your doctor. Please wait between intake of calcium/magnesium salts and MPA: • Magnesium/calcium – solid formulation: Wait 2 hours • Magnesium/Calcium – liquid formulation: Wait 1 hour • Minerals: Wait 30 min Limit sunlight and wear UV protection. Please report all side effects to your doctor. Side effects can include: Diarrhoea, urinary tract infections, tremor, hypertension, headache, insomnia, fever (list not complete). There are some interactions between MPA and other drugs. To avoid problems have your medication checked by a doctor or pharmacist	
Omeprazole	Reduces stomach acid production	Can reduce nausea and vomiting during dose increases of cysteamine	Dark and dry (not in the bathroom) between 20°C and

		treatment. Check your vitamin B ₁₂ status during long-term treatment. Take on empty stomach in the morning or very late in the evening	25°C (68°F and 77°F)
Pantoprazole	Reduces stomach acid production	See Omeprazole	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Phosphate salts • sodium • potassium	Treats phosphate deficiency	Between intake of phosphate and calcium you should wait: • Liquid calcium and liquid phosphate: 30 min in between • Liquid calcium and solid phosphate (capsules or tablets): First calcium, 30 min later phosphate • Liquid phosphate and solid calcium (capsules or tablets): First phosphate, 30 min later calcium • Solid calcium and solid phosphate: 2 hours in between each Phosphate salts can be mixed with sodium and potassium salts, if necessary (not calcium and magnesium)	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Potassium salts • chloride • citrate	Treats potassium deficiency	Potassium chloride: To avoid nausea and vomiting, dilute in water or juice. Potassium salts can be mixed with calcium, sodium, and magnesium salts, if necessary. Use of potassium should be distributed throughout the day. Potassium citrate: Please wait 30 min between intake of potassium citrate and Procysbi®. You can dilute	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F). Shelf life of potassium salts after dissolving in water: 24 hours

		potassium salts in a bottle of water or juice to mask a taste	
Pravastatin	Lowers cholesterol level	See Atorvastatin	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Rosuvastatin	Lowers cholesterol level	See Atorvastatin	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Simvastatin	Lowers cholesterol level	See Atorvastatin. Take in the evening (morning use not possible)	Dark and dry (not in the bathroom) between 20°C and 25°C (68°F and 77°F)
Sodium salts • hydrogen carbonate • chloride • citrate	Treats sodium deficiency	Sodium hydrogen carbonate liquid ('baking soda')/sodium chloride: To avoid nausea and vomiting, dilute in water or juice. Sodium salts can be mixed with calcium, potassium, and magnesium salts, if necessary Allow 30 min between sodium hydrogen carbonate and Procysbi® use.	Shelf life of sodium salts after dissolving in water: 24 hours
Somatropin (growth hormone)	Treats growth deficiency	Due to delivery bottlenecks, it may be necessary to exchange preparations. Talk to your doctor or pharmacist about this – these products are comparable, but they are differently tolerated in some patients	Unopened vials: Between 2° and 8°C (36°F and 44°F) (refrigerator) – do not freeze!
Tacrolimus	Prevents the rejection of organ transplants	Avoid combination with pineapple, bitter orange, pomelo, or alcohol. There are different dosage forms	Dark and dry (not in the bathroom) between 20°C and

		(capsules vs tablets vs oral suspension; immediate release vs extended release) – these forms are not interchangeable. Sometimes you will have different forms at the same time – please check the medication plan or ask your doctor or pharmacist to avoid administration errors. Tacrolimus should be taken on an empty stomach with water. Do not change the intake procedure to avoid blood level fluctuations. African-American patients, compared with Caucasian patients, may need to be titrated to higher tacrolimus doses to attain comparable trough concentrations – ask your doctor for advice. Please report all side effects to your doctor. Side effects can include diarrhoea, urinary tract infections, tremor, hypertension, headache, insomnia, and fever (list not complete). There are some interactions between tacrolimus and other drugs. To avoid problems, ask your doctor or pharmacist to check your medication	25°C (68°F and 77°F)
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Over-the-counter (OTC) medications, herbs, and supplements

As the management of patients with nephropathic cystinosis can be complex and require the use of differing treatments, interactions with herbal and dietary supplements, along with OTC medications, are possible.

Please inform your doctor about all non-prescription products you or your child are taking. Ask your pharmacist about potential interactions before using any herbal and dietary supplements, or OTC medications.

Medication	Use	Safety	Alternative (s)
Non-steroidal anti-inflammatory drugs (NSAIDs) - Ibuprofen - Diclofenac - Naproxen	Pain, fever	NSAIDs reduce the blood flow in the kidney. They are generally not recommended in patients with kidney disease Please ask your doctor or pharmacist before taking it. Short-term use is conceivable, although sufficient fluids should be consumed	Paracetamol Metamizole (if available in your country)
Cough syrup	Flu, cold, cough	Avoid taking	Consult with your pharmacist about alternative medicines - Decongestant nasal spray (Xylometazoline) - Topical flu creams (essential oils) - Saline nasal spray - Paracetamol
Cough medicine - Dextromethorphan - Pentoxyverine	Cough (dry)	Dextromethorphan: Take care when using and check for possible interactions with any prescribed medicine(s) (check with pharmacist prior to use) Children aged less than 2 years: Consult your doctor prior to use Pentoxyverine: No data available for patients	- Warm milk with honey (30 min between phosphate medications) - Topical flu creams (essential oils)

		with poor kidney function – consult your doctor	
Herbs (infusion, capsules, tablets) • Coneflower (Echinacea species) • St. John's wort • Licorice (glycyrrhiza glabra)	Immune system, depression, fear Cough/flu	Echinacea purpurea: Avoid if a kidney has been transplanted St. John's wort: Avoid if a kidney has been transplanted Licorice: Avoid as this can influence potassium levels	• Zinc citrate 10 mg per day (also possible after kidney transplantation) • If you have symptoms of depression, please consult your doctor • Thyme, sage, and peppermint can be used
Antacids • Calcium salts • Magnesium salts • Aluminium salts	Gastric reflux, heartburn	Calcium, magnesium, and aluminium can interact with some medicines: Avoid or consult your doctor or pharmacist prior to use	• Sodium alginate (Gaviscon®)
Anti-allergy drugs	Allergy	These medications should only be used in consultation with a nephrologist	• Azelastine nasal spray/eye drops • Corticosteroid nasal spray/eye drops
Topical creams (applied externally)	Various	Topical creams are generally safe	

Patient organisations

Clinical guidelines and further information are already available for some of the topics covered in this guideline. The clinical S3-guideline for cystinosis provides a comprehensive bibliography for public use.

A review of the literature on general topics related to kidney disease can be found on the homepage of the European Network for Rare Kidney Diseases ERKNet. This website can be read in 11 different languages.

<https://www.erknet.org/patients/what-is/erknet>

If you are looking for further information and explanations on cystinosis in general and on specific topics, the European and national cystinosis patient organisations provide informative homepages and encourage personal contact.

Cystinosis Network Europe	www.cystinosis-europe.eu
Asociación Cistinosis España	www.grupocistinosis.org
Associazione Cistinosi, Italy	www.cistinosi.it
Cystinosis Foundation UK	www.cystinosis.org.uk
Cystinosis Ireland	www.cystinosis.ie
Cystinose-Selbsthilfe e.V., Germany	www.cystinose-selbsthilfe.de
Dutch and Flemish Cystinosis Group	www.cystinose.nl
Cystinosis Foundation South Africa	www.cystinosis.co.za
Cystinosis Research Network USA	www.cystinosis.org
Cystinosis Research Foundation USA	www.cystinosisresearch.org
Cystinosis support Australia	www.cystinosis.com.au
Cystinosis support group Turkey	
Mexican Association of Cystinosis	www.cistinosis.org.mx
Vaincre les Maladies Lysosomale (VML France)	www.vml-asso.org

Supplementary Box 2. Cystinosis Metabolic Bone Disease (CMBD)

CMBD can present with short stature, osteomalacia, bone deformities, kyphos-scoliosis, bone pain, flat feet, in children with rickets and in adults with long bone fractures, incidental vertebral fractures, scoliosis, low bone mass, and cortical impairment.

- **Renal Fanconi syndrome resulting in rickets due to**
Metabolic acidosis, hypophosphatemia, hypocalcaemia, 1,25-dihydroxy vitamin D deficiency
- **Deficiency in nutrition and micronutrition**
Malnutrition, copper deficiency
- **Hormonal disturbances**
Hypothyroidism, hypoparathyroidism, hypogonadism, growth hormone, and insulin-like growth factor 1 resistance
- **Myopathy**
Cystine accumulation in striated muscles, inflammation
Hypophosphatemia, hypocalcaemia
- **Intrinsic and treatment-associated bone lesions**
Cysteamine toxicity, inflammation
Intrinsic osteoblast/osteoclast defect due to *CTNS* mutation
- **Mineral and bone disorders due to chronic kidney disease-mineral and bone disorder (CKD-MBD)**
Hyperphosphatemia, hypocalcaemia, 25-hydroxy vitamin D deficiency, 1,25-dihydroxy vitamin D deficiency
Secondary hyperparathyroidism
- **CKD-MBD post-transplantation**
Glucocorticoid and calcineurin inhibitor treatment
Hypophosphatemia due to persistent Fanconi syndrome
Mineral and bone disorders related to transplant dysfunction

Supplementary Box 3. Anamnestic questions to assess the presence of dysphagia (ask at least once/year)

- Do you have difficulties swallowing your medications?
- Do you have problems swallowing your saliva?
- Do you have problems swallowing water?
- Do you have the sensation of food stuck in your throat when you eat?
- How long does it take to complete your meal?
- Do you need to drink during meals to empty your mouth?
- Do you often have to clear your throat?
- Do you experience coughing or shortness of breath during and after eating or drinking?
- Is your voice altered during or after eating or drinking?
- Do you experience episodes of choking?

Supplementary Box 4. Cysteamine eye-drops

- Cysteamine-HCl 0.1%
Recommended frequency of instillation: Every hour during waking hours
- Cysteamine-HCl 0.2%
Recommended frequency of instillation: 6 times per day
- Cysteamine-HCl 0.55%
Recommended frequency of instillation: 10 times per day; at least 6 times per day
- Cystaran™ (Cysteamine-HCl 0.65%)
Recommended frequency of instillation: 8–12 times per day
- Cystadrops™ (Cysteamine-HCl 0.55%, gel-like formulation)
Recommended frequency of instillation: 4 times per day