Information for General Practitioners about

Cystinosis

VSOP

Zeldzame Ziekten

CYSTINOSE Groep Nederland

VKS Volwassenen, Kinderen en Stofwisselingsziekten

nhg nederlands huisartsen genootschap

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Introduction

Having a rare, chronic condition means that in many cases people have frequent contact with various healthcare providers over a long period of time. Medical specialists and general practitioners have an important role in providing high-standard medical care and in fulfilling different needs. Therefore, both patient and general practitioner need to be familiar with the condition. This brochure is for general practitioners and other health care providers who take care of patients with cystinosis. The content is of particular importance after the diagnostic phase.
For more specific questions: contact the physician - specialist responsible for treatment management.

Origins

This brochure was created as a collaborative effort between Dutch Cystinosis Group (member of VKS: Adults, Children and Metabolic Diseases), the Collaborative Association of Parent and Patient Organisations (VSOP) and the Dutch College of General Practitioners (NHG).

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Cystinosis

Cystinosis is a rare metabolic disease characterised by a defect in the lysosomal transporter protein cystinosin, resulting in the accumulation of cystine. The condition is caused by mutations in the *CTNS* gene which is expressed in all tissues. Cystinosis is an inherited, autosomal recessive disorder. The accumulation of cystine in lysosomes leads to cell death and other pathological processes, leading to a multi-organ disease. The kidneys are especially sensitive to cystinosin dysfunction. When left untreated, nephropathic cystinosis leads to end-stage renal failure in the first decade of life. In addition to kidney problems, most patients suffer from photophobia, hypothyroidism, muscle weakness, hypergonadotrophic hypogonadism (males), reduced growth and severe fatigue.
Life expectancy has improved dramatically since the advent of renal transplantation. In addition, the development of cysteamine that decreases lysosomal cystine accumulation, has led to a delay in the disease progression and also to an increase in life expectancy and quality.[3,8,13] Cysteamine is available in an immediate-release format - Cystagon™ and in some countries in a delayed-release format - Procysbi ™.

Facts

Prevalence

- The incidence of cystinosis is approximately 1:100.000-200.000 live births.[3,8]
- There are 10 to 15 new cases of cystinosis diagnosed each year in Europe.[12]
- A general practitioner with an average standard practice that operates for 30 years, will probably not see more than one patient with cystinosis. Because cystinosis is a genetic disorder, there will be sometimes multiple patients from one family.

Heredity and aetiology

- All forms of cystinosis (see *Clinical Forms*) are caused by a defect in the *CTNS* gene which is located on chromosome 17p13. At least 100 different mutations have been reported.
- Cystinosis is an autosomal recessive inherited disease. Heterozygotes are symptom-free, but can have slightly elevated cellular cystine content.[3,8]
- The protein product of the *CTNS* is cystinosin, which ensures the transporting of cystine out of the lysosome. The gene is expressed in all cells. Intralysosomal accumulation of cystine leads to the formation of crystals. The tubular kidney tissue is the most sensitive to cystinosin accumulation.[3,1]

Clinical Forms

There are three forms of cystinosis: :

- **Infantile or classic cystinosis** This is the most severe and most prevalent form of cystinosis (95%). The brochure focuses mainly on this form of cystinosis.
- **Intermediate cystinose, or late-onset cystinosis** This form has most characteristics of the infantile cystinosis, but starts at a later age (adolescence).
- **Ocular cystinosis** is characterized by crystal formation in the cornea and photophobia, without other manifestations of cystinosis.[8]

Diagnosis

The infantile form manifests at an age of between 3 and 6 months with renal Fanconi syndrome (note: this is not Fanconi anaemia). Fanconi syndrome is characterized by dysfunction of the proximal tubules in the kidneys, whereby nutrients and electrolytes are not properly reabsorbed and are excreted with the urine. This leads to nutritional problems and impaired growth ('failure-to-thrive') in combination with excessive urination and drinking of water (rather than milk) and/or dehydration, vomiting, constipation and often signs of rickets. In laboratory tests, there is metabolic acidosis in conjunction with hypokalaemia, hypocalcaemia, hypophosphatemia, hypoalbuminemia, low uric acid and carnitine. Urine examination shows aminoaciduria, glucosuria, proteinuria (albuminuria and low molecular weight proteins).
From the age of one year, cystine crystals can also be observed in the cornea with a slit lamp examination. The diagnosis can be made by measuring cystine in leukocytes (LCL, normal is 0.04-0.12 nmol/mg protein and in patients with cystinosis this will be above 1 nmol/mg protein) confirmed by genetic diagnostics. Serum creatinine is often normal in young children, but can increase drastically after 5 years, particularly without or insufficient cysteamine treatment.
It is very important to make an early diagnosis to ensure early start of the treatment (also see *Progression*).[3,8]

Early cysteamine treatment means slower onset of renal failure and amelioration of symptoms such as growth retardation, etc.

Progression

Left untreated, cystinosis leads to end-stage renal failure before the age of 10 years. Renal replacement therapy (dialysis or transplantation) improves survival. However, other disease manifestations become apparent later in life. The accumulation of cystine continues in all organs and leads to a multi-organ disease (also see *Symptoms*).

The drug cysteamine ensures transportation of cystine out of the cell. Correct intake of the drug helps to prevent progression of cystinosis. This usually delays the need for renal replacement therapy until the 2nd or 3rd decade of life and protects extra-renal organs.[8] Good cysteamine adherence from an early age (<2 years) can reduce considerably the adverse symptoms described below (See *Symptoms*).

Symptoms

Clinical manifestations of cystinosis can be roughly divided into symptoms deriving from the kidneys and from other organs.

Renal symptoms

During the early phase of the disease, kidney problems are caused by reduced functioning of proximal tubules (renal Fanconi syndrome).[3,8]

When left untreated also the glomural capillaries are affected leading to a severe reduction in renal function, resulting in end-stage renal disease (ESRD) at the age of 7 to 10 years. Treatment with cysteamine can delay ESRD until puberty or young adulthood.[8]

- **Polyuria (excessive urination)** In children, this leads to frequent dehydration, for example during warm weather or periods of viral infections such as influenza or other upper respiratory tract infections, or gastroenteritis. Children suffer from thirst and drink a lot (polydipsia). They show preference for water (instead of milk). Together with decreased appetite, this can impede the intake of nutrients, resulting in malnutrition and poor growth.[3,8]
- **Vomiting** Renal electrolyte losses lead to general malaise and vomiting. Severe hypokalaemia can lead to a paralytic ileum or constipation. Vomiting and nausea cause a reduced intake and increased excretion of nutrients.[3]
- **Constipation** This is caused by fluid deficiency (as a result of polyuria), by reduced intake of food and by hypokalaemia. Severe constipation can lead to a distended abdomen and nutritional problems.[3]

The three symptoms mentioned above lead to **nutritional problems** in children with cystinosis. Currently, PEG catheter (percutaneous endoscopic gastrostomy) is placed in the majority of the children. This can be used for medication, fluid and nutrition.

- **Failure-to-thrive** Because of the above-mentioned symptoms, children with cystinosis grow poorly. Normal development can be also compromised.[3,8]
- **Rickets** This is caused by phosphate losses and decreased calciferol (vitamin D).[3,8] Cystinosis children can present with bone pain, gene vara (bow-legs), frontal bossing, rachitic rosary (beading of the ribs), delayed closure of the large fontanelle, a large rectangular head, carinate chest deformity, scoliosis and dental development disorders.
- **General malaise and fatigue** can be caused by progressing renal insufficiency, which eventually leads to ESRD.[8]

Other symptoms

- **Behavioural problems** and mood changes often occur. This is partly due to fatigue and other physical symptoms.
- **Learning disabilities** can manifest already in some young children. They are mainly caused by **visual-spatial problems** and some degree of fine motor skills limitations. Other cognitive functions are usually preserved.[2,3,8,10]
- **Eye problems** Cystine crystals accumulate in the cornea. Using a slit lamp examination, the ophthalmologist can observe these crystals after the age of 1 year. Cystine crystal accumulation increases with age. Cystine crystals cause photophobia and red or watery eyes. Specific abnormalities of the cornea and also in the retina can develop.[3,8]
- **Heat sensitivity** Reduced sweating can lead to hyperthermia.[8] In addition cystinosis children dehydrate more rapidly due to polyuria.
- **Muscle weakness** The accumulation of cystine in the muscles can lead to muscle weakness.
- **Fatigue is frequent** This is probably the consequence of different medical problems.
- **Distal myopathy** is progressive with swallowing problems and pulmonary dysfunction as late complications. This distal myopathy and oromotor dysfunction can occur in young adults due to accumulation of cystine in the smooth muscles.[3,8]
- **Bone problems** such as fractures occur more frequently in cystinosis patients (also see *Treatment*).
- **Pulmonary dysfunction** can arise due to severe muscle involvement. This can lead to severe exercise intolerance and respiratory problems.[3]
- **Swallowing problems** can arise due to myopathy of the oropharyngeal muscles.[3,8]
- **Aspiration** Pneumonia is a real danger in patients (usually adults) with restrictive lung dysfunction in combination with the swallowing problems.[8]
- **Kidney stones (nephrocalcinosis)** rarely occur, and are caused by high calcium and phosphate excretion.[8]
- **Pale skin and blond hair** is characteristic. Children are often blond or have lighter complexion than their parents.[5,12]
- **Bruising** arises easily and heals less quickly.
- **Hypothyroidism** arises in 75% of untreated patients after the age of 10 years.[3]
- **Hypergonadotropic hypogonadism** can arise in boys only. Administration of testosterone helps ensure that these boys can enter puberty. Unfortunately, this treatment does not prevent fertility problems.[3,8]
- **Delayed puberty** can also occur in girls, but their gonadal function is not as severely affected as in boys. Successful pregnancies have been reported. On average, in cystinosis children there is a puberty delay of 1-2 years.[3,8]
- Other **endocrinopathies** can also occur such as hyperprolactinemia.[1]
- **Insulin-dependent diabetes mellitus** can develop due to pancreas dysfunction. This complication can occur in the teenage years (and after kidney transplantation).[3,8]
- **Hepatomegaly** and **splenomegaly** occur in approximately 30% of the patients above fifteen years. When patients are inadequately treated with cysteamine, nodular

regenerative hyperplasia of the liver might occur with portal hypertension as a consequence.[2,3,8]

- **Headache and papilledema** can arise due to benign intracranial hypertension.[8]
- **Hypertension** can arise in consequence of the renal damage and might persist after transplantation. Some patients also have **hypercholesterolaemia** with vascular calcifications, coronary sclerosis and cardiomyopathy.[8]
- **Involvement of the central nervous system** is a late complication in approximately 10% of the patients and includes speech limitations, memory loss, reduced intellectual functions and dementia due to accumulation of cystine in the basal ganglia.[3,8]
- Many **psychosocial aspects** play a role in cystinosis. These patients have been seriously ill since infancy and they are subjected to many hospital visits, admissions and invasive treatments. In addition, the strict medication regimen (every six hours) leads to disturbed sleep of both parents and patients. Due to fatigue, patients can be engaged in less activities. This can have consequences for school, the choice of job, and for social contact and relationships.

Efficacy of cysteamine

The severity of the symptoms depends on the effectiveness of treatment with cysteamine. Patients who do not take cysteamine experience more severe symptoms. In one study 100 patients were monitored of whom 39 were adequately treated with cysteamine. The following bar chart clearly shows the differences between adequately treated patients and untreated or inadequately treated patients.[4]

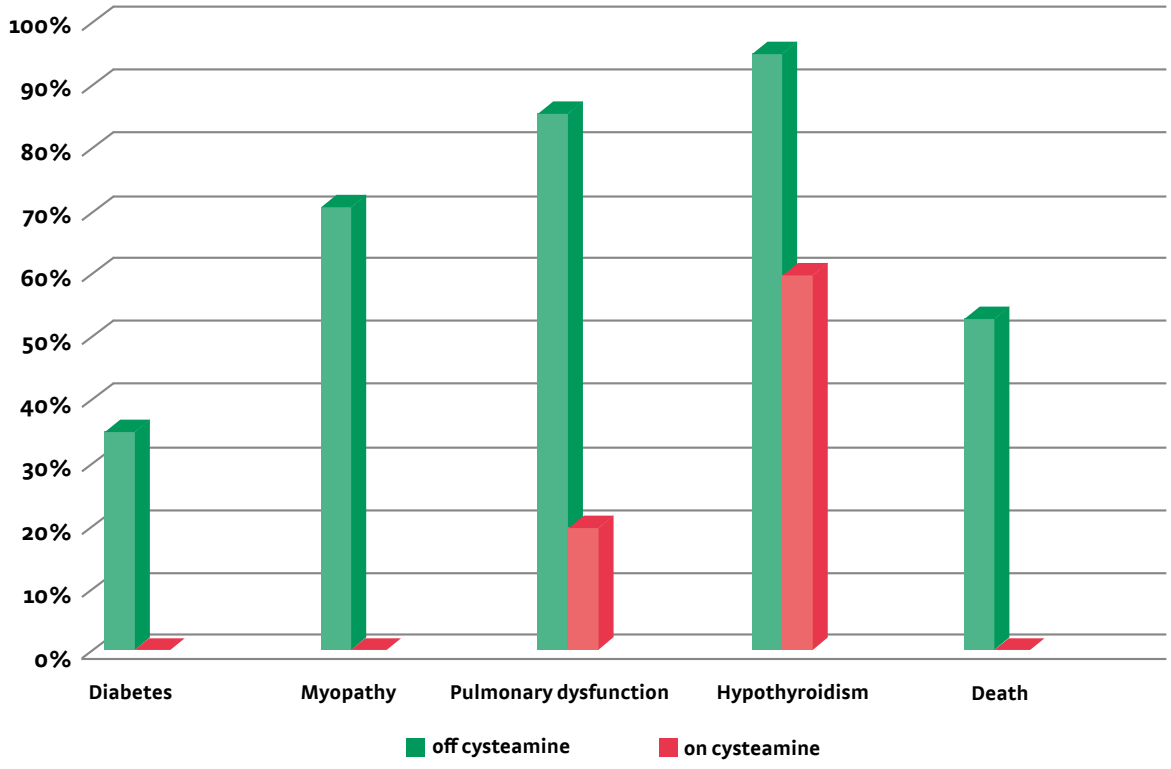

Figure 1: Percentage of cystinosis patients with diabetes, myopathy, pulmonary dysfunction and hypothyroidism **between 21 and 30 years old**. 61 untreated patients (green) and 39 patients adequately treated with cysteamine (red). The right side also shows the number of patients that survive without treatment.[4]

Management

Care coordination

Children with cystinosis are usually treated by a paediatric nephrologist. Adult patients are mostly followed by a nephrologist for their kidney graft and in some countries by an internist specialized in metabolic diseases.

- **Transition from paediatric to adult care** is a precarious process, which is best done in a cystinosis centre of expertise (see *Consultation and Referral*).
- A **multidisciplinary approach** is very important, especially with regard to the multi-organ nature of cystinosis. In any case, a nephrologist, ophthalmologist, internist in metabolic diseases and if required, an endocrinologist, a social worker and/or neurologist should be involved. Such care can be provided in a cystinosis reference center (see *Consultation and Referral*).

Monitoring

After diagnosis, patients are followed approximately every three to six months for monitoring. Because cystinosis is a multi-organ disease, a broad evaluation is necessary.
The parameters to follow are:

- Height/weight/blood pressure/physical examination;
- Blood tests for renal function, electrolytes, hepatic function and thyroid function, Ca and P metabolism;
- LCL (leukocyte cystine level): one (in adults) to four times (in children) a year to adjust cysteamine doses (see *Treatment*);
- Ultrasound of the kidneys (screening for nephrocalcinosis);
- Rx hand (children for bone age);
- Check-up by an ophthalmologist (slit lamp examination for crystal formation in the cornea, optical coherent tomography (OCT), in vivo confocal microscopy (IVCM) in some centres of excellence).

Treatment

The treatment of cystinosis consists of three pillars:

- treatment with cysteamine;
- treatment of renal problems:
  - Fanconi syndrome;
  - renal replacement therapy (dialysis and/or transplantation).
- treatment of extra-renal complications.

Given the seriousness of the condition, **psychosocial help** forms an important part of the treatment in all life phases (see *Considerations for the general practitioner*).

Treatment with cysteamine

The cornerstone of the treatment is the administration of cysteamine. This drug ensures the removal of cystine from the cell. This treatment should start as early as possible and should be continued life-long. This will not completely stop disease progression, but it improves the prognosis considerably. Excellent adherence to the treatment leads to postponement of end-stage renal failure by 6 to 10 years and to delay or even prevention of extra-renal organ damage.[3,8]
The most commonly used drug is cysteamine bitartrate. This drug should be taken every six hours or can be administered via a PEG catheter, also at night. Cysteamine can cause severe gastrointestinal side effects. Because of this the paediatrician will gradually increase the dose in the beginning. However, gastrointestinal upset and vomiting can still occur for many years. A further side effect is body odour and halitosis (bad breath described as 'rotten eggs'). Riboflavin (vitamin B2) or chlorophyll tablets can possibly mask this odour.[3]

In some countries, an enteric coated, delayed-released formulation of cysteamine is available. This enables a 12-hourly dose which allows for uninterrupted sleep. Also the total dose is slightly lower.

The dose of cysteamine will be adjusted based on the LCL (leukocytes cystine levels). This test can only be done in a few specialized laboratories. Inadequately low cysteamine doses lead to the further accumulation of cystine.

Some patients treated with high cysteamine doses or who have increased sensitivity to cysteamine can experience the following side effects:

- swelling on the elbows, resembling scar tissue or bruising; some elbow swellings resemble 'blood blisters';
- severe bone pain and bone deformities;
- red stretch marks (striae) on the outside of arms and legs;
- muscular or neurological symptoms, such as myopathy or hypermobility of the joints.[3]

For these symptoms, the healthcare provider (general practitioner/paediatrician/internist/other) should promptly contact the centre of expertise (see *Consultation and Referral*).

- **Cysteamine eye drops** Oral cysteamine does not have any effect on the development of cystine crystals in the cornea, because the cornea is not vascularized. Therefore patients are advised to use cysteamine eye drops ideally every waking hour, but at least 6 times daily. A new viscous formulation (Cystadrops) is available since 2017 with a 4 times/day dosing scheme. The drops can cause an intense burning sensation. Untreated, the cystine accumulation can lead to extensive cornea damage which can cause corneal blindness.

Treatment of renal problems

Treatment of **renal Fanconi syndrome** consists of adequate nutrition, fluid administration and substituting urinary losses (minerals and bicarbonate). This is crucial for the growth of the child.[3,8]

- **Diet** is an important component for the treatment of Fanconi syndrome. The diet should be balanced, with adequate caloric content, and should contain sufficient amount of fluid and salts. All patients should be followed by paediatric dieticians.[3,8]
- In many children, a **PEG catheter** is placed as soon as possible after the diagnosis because children cannot get sufficient calories due to vomiting and lack of appetite. The caloric intake must be 100% of age requirements. There is no evidence that higher intake will lead to better growth. A PEG catheter can also help to administer **extra fluids** and to give medications during the night.[2] With renal insufficiency, a protein-restricted diet is often necessary. The treatment of **rickets** consists of supplementation with phosphate in combination with vitamin D. Alfacalcidol (the active form of vitamin D) should also be given.
- Other **bone problems** such as genua valga and pedes plani can develop at a later age (> age 5 years) . The aetiology of these problems is multi-factorial and can also be due to copper deficiency. Copper supplementation in these patients should be considered. Bone fractures are also more common in cystinosis patients.
- **ESRD** finally occurs in all patients. Kidney transplantation is far more preferable than dialysis, considering the quality of life and the effects on health. Both live and post-mortem transplantations are performed. The disease doesn't recur in the kidney graft as the genetic defect is not present in the graft, but cystine crystals might be observed in the donor kidney due to invasion by host cells.[3,8]
- Cysteamine stimulates acid production in the stomach and **proton pump inhibitors** can improve gastric problems.
- **Indomethacin** inhibits prostaglandin synthesis in the renal parenchyma. This limits the loss of fluid and salts. However, the drug can cause severe stomach complaints and acute renal insufficiency. Despite these severe side effects, paediatric nephrologists regularly prescribe the drug to have better control over Fanconi syndrome. Nevertheless, the general practitioner or paediatrician should, in consultation with the paediatric nephrologist, advise the patient to immediately discontinue the medication in case of dehydration, hypotension, the necessity to use ACE inhibitors (*enalapril*, *Lisinopril* etc) or in case of deterioration in the renal function.[3]
- **ACE inhibitors and angiotensin receptor blockers** should be prescribed with caution by (paediatric) nephrologists due to the potential side effects (see *Considerations for the general practitioner, Alarm symptoms*). These drugs appear to protect the kidney in patients with proteinuria. However, they also cause a reduction in renal perfusion. High doses must be avoided. In warm weather, or with high fever or gastroenteritis the healthcare provider (general practitioner/paediatrician/internist/ other) will advise to skip a dose or discontinue the drug. In these situations the general practitioner should contact the responsible nephrologist to discuss treatment options.[3,8] Parents should be informed about these risks.
- **Growth hormone** The treatment with cysteamine in combination with sufficient intake ensures adequate growth in many children. However, it does not guarantee a 'catch-up' growth. When cysteamine, adequate nutrition and metabolic control cannot obviate growth retardation, growth hormone treatment should be initiated. This has the most effect when started early, prior to renal replacement therapy. Long-term growth hormone administration ensures adult height of at least between -2.5 and -2.0 SD.[3,8]
- **Testosterone** Many boys with cystinosis develop a hypergonadotropic hypogonadism. Administration of testosterone can help to stimulate puberty. Unfortunately, testosterone does not prevent fertility problems.[2] In male patients willing to have children percutaneous epididymal sperm aspiration (PESA) followed by intracytoplasmatic sperm injection (ICSI) can be a successful procedure. (Veys et al. JIMD 2017).

Renal replacement therapy (dialysis and/or transplantation)

Renal replacement therapy is unavoidable in the majority of patients. Decreased kidney function leads to even more symptoms of general malaise with nausea and fatigue. The (paediatric) nephrologist will initiate preparations for renal replacement therapy when renal function is 25-30% of normal. This includes preparations for a possible transplant (if there are suitable living donors (kidney donation from live subjects gives a better result than post-mortem donation)), check vaccination status (hepatitis B and chickenpox). Timely preparation reduces stress and ensures transplantation before starting dialysis when a living donor is available. When kidney function further deteriorates, the nephrologist will place the patient on a waiting list for a post-mortem kidney transplantation, and start dialysis. Life-long immunosuppressant drugs are necessary after the transplantation to prevent rejection of the graft.
Side effect of immunosuppressive treatment after kidney transplantation are increased susceptibility to viral and mycotic infections, malignancies, diabetes, fatigue. Migraine-like headache is often seen after transplant.

Possible future treatments

Current research in cystinosis mouse model shows that a combination of stem cell transplantation and gene therapy could cure the disease. However, it still has to be tested whether this therapy can cure human disease.[6,9]
Cysteamine eye drops can be prepared by some hospitals pharmacies. These drops should be used at least 6 times

daily (ideally every waking hour) to prevent the formation of corneal crystals. In practice most patients use eye drops less frequently (4 to 5 times daily).
Since 2017, viscous eye drops with cysteamine (Cystadrops®) are available in Europe. This gel has to be administered 4 times daily.

Treatment policy for Emergency Room (ER) or doctor's surgery

Patients frequently come to emergency room because of infections, dehydration or bone fractures.

- **Dehydration** Immediately start IV infusion with isotonic fluid or possibly with glucose and/or ringer lactate.
- When **urinary tract infection is suspected** urine has to be collected for testing urine sediment and culture, and amoxicillin clavulanic acid or a 3rd generation cephalosporin should be administered. Based on the renal function and other medications used (e.g. immunosuppressants), the dose of the medications should be adjusted.
- **Bone fracture** In the case of a bone fracture it is important to ensure adequate pain medication. NSAIDs are strongly discouraged in cystinosis patients, given the danger of acute renal insufficiency. Paracetamol or a morphine derivative should be used when necessary. Certainly in children, pain relief is of the ***utmost importanc*e** to obviate mental trauma. Dipidolor (0.2 mg/kg/dose (max. 20 mg)) does not need to be adjusted to the renal function as it is metabolised in the liver. In addition, little interaction with the majority of immunosuppressants is expected.

Genetic counseling and pregnancy

Familial investigation

- Cystinosis is an autosomal recessive disorder (see *Facts, Heredity and aetiology*).
- The paediatric nephrologist or clinical geneticist will discuss the hereditary aspect of cystinosis with the patient and/or the parents. In nearly all cases, both parents are carriers of the *CTNS* gene mutation. The risk of having an affected child in these families is 25% for each conception. DNA testing (genetic analysis of the *CTNS* gene) can confirm the carrier status.
- **Right of self-determination** It is important that the desirability and/or the consequences of DNA testing are extensively discussed and sufficient time is provided for decision making. Aside from the right to know, patients and family members also have the right not to know.
- **Informing family members** In certain countries, legislation does not permit clinical geneticists/councillors to directly inform family members about the existence of a (severe) genetic disorder in their family. However, the patient is entitled to inform family members with the guidance of clinical geneticists and the aid of a letter for the family members.

Family planning and pregnancy

- During the use of the immunosuppressant mycophenolate mofetil (or other mycophenolic acids) the prevention of pregnancy is important for both men and women, because of teratogenicity of the drug. The medical practitioners involved (nephrologist, general practitioner) should inform patients about this risk.
- Family planning in female cystinosis patients. Refer female patients with cystinosis to an obstetrician/gynaecologist specialising in the guidance of pregnant renal patients for preconception advice.
- Treatment with cysteamine will have to be interrupted during pregnancy and during the period of lactation. The pregnancy will also be supervised by the specialist gynaecologist. Use of ACE-inhibitors should also be discontinued during pregnancy.
- Family planning in male cystinosis patients. Many men with cystinosis have hypergonadotropic hypogonadism and therefore azoospermia. Men can have sperm cells harvested for purposes of inducing a pregnancy. Do not hesitate to refer to a clinical geneticist and/or fertility centre for preconception advice.
- If parents who are carriers of the cystinosis gene are considering **having more children**, the attending paediatrician/nephrologist or clinical geneticist can inform them about the level risk of future children having cystinosis and can also discuss the possibilities of prenatal diagnosis or pre-implantation genetic diagnostics

Prenatal diagnosis

- **Chorionic villus sampling or amniocentesis** Parents can have prenatal testing of cystinosis, using chorionic villus sampling at 11-12 weeks of pregnancy. An amniocentesis at approximately 15 weeks of pregnancy is also possible. These tests are mainly done when there is already a child with cystinosis in the family. The cystine level in the chorion villi or amnion cells can also be determined.
- **Pre-implantation genetic diagnosis** If parents decide they want to undergo pre-implantation genetic diagnosis (PGD), the general practitioner or nephrologist will refer them to the clinical geneticist for counseling. After fertilisation using IVF procedure, one or more cells are taken from the embryos and examined for the presence of the CTNS gene mutation. After testing, one or two non-affected embryos are placed in the uterus.

Considerations for the general practitioner

General points for consideration

These points can be applied to patients suffering from different rare diseases.[7,11]

- Actively approach the patient or parents as soon as the diagnosis of a rare disease is known.
- If necessary, ask how the parent/patient experienced the general practitioner's approach in the phase prior to the diagnosis. Then review how this approach or the general practitioner's attitude affected the doctor-patient relationship.
- Ask to what extent the patient and family members accepted the diagnosis. Repeat these questions during subsequent visits and check whether the family is successfully coping with the disease.
- Discuss with the patient and/or the parents what can be expected from the general practitioner in terms of treatment and guidance.
- Ensure that locum general practitioners (including GP of emergency ward) are acquainted with the patient and the special characteristics and circumstances of the disease.
- Ensure that you have sufficient knowledge in the disorder (see *Specific points for consideration*). In case of doubts, consult the responsible specialist.

Specific points for consideration

- **Medication** In patients with renal insufficiency, not all drugs are allowed, or dose adaptation is required. If necessary, consult the pharmacist or the nephrologist about this matter.
- **Influenza vaccination** Considering the impaired resistance, influenza vaccination should be offered.
- **Developmental delays** Because of the lack of energy, motor skills development might be lagging. Do not hesitate to refer to a paediatric physiotherapist and/or occupational therapist.
- **Other children in the family** The presence of glycosuria and proteinuria in a child with normal blood glucose indicates the presence of renal Fanconi syndrome (for example in brothers, sisters or nephews/nieces, see *Facts, Diagnosis*).
- **Genetics and pregnancy** A proactive attitude of the general practitioner is of major importance. Do not hesitate to refer to a clinical geneticist in case of a (new) desire to have children in families who already have a child with cystinosis, or to a specialised gynaecologist and clinical geneticist in case of pregnancy (see *Heredity explanation and Pregnancy*).
- **Volunteer aid** Caring for a chronically ill family member is burdensome. Actively enquire from parents/guidance counsellors whether they require psychological support and/or, for example, household assistance/nursing/caring/guidance.
- Children with cystinosis **drink a lot** and have **poor appetite** which makes it difficult to attain adequate caloric intake. A PEG catheter is readily prescribed for these children. Patients with Fanconi syndrome have salt craving which should not be discouraged. The ingestion of additional salt does not necessarily lead to additional kidney damage in this case.

Patients need to have permanent, unrestricted access to drinking water.

- **Excessive urination** Because of polyuria it is difficult to achieve continence, especially during the night. Aid of specialized continence nurses might be helpful. High bladder volumes must be prevented by regular voiding.
- **Fatigue** occurs in many patients, even after transplantation. If necessary, refer for occupational therapy (to better adapt daily life) and/or physiotherapy (for retention of fitness).
- **Dry painful eyes** can occur. It is difficult to maintain the regimen with aqueous cysteamine eye drops (very frequent application in combination with the burning sensation). Readily refer to the ophthalmologist for supplementary advice.

Alarm symptoms

- **Dehydration** Because of the specific kidney problems, (young) children dehydrate easily. This can occur during warm periods and especially during episodes of fever or vomiting. It is important to readily consult with or refer patients to the reference centre. Also check whether the child is using indomethacin and/or enalapril; these medication should be stopped in patients at risk of dehydration. Consult the paediatrician for advice.
- **Infections** After a kidney transplant, patients are susceptible to infections because of the use of immunosuppressants. Readily prescribe antibiotics/antifungals.
- **Bone fractures** can occur more frequently in patients with cystinosis. Regular care in the emergency room is recommended. However, it is very important that the correct pain relief is started immediately: paracetamol and/or morphine (no NSAIDs because of the decreased renal function). Also see *Treatment Management*, *Emergency Assistance (ER)* or *doctor's surgery*.

Psychosocial aspects

- Having a child with a chronic (severe) disorder often entails the risk of **parents being overburdened**. The child has to undergo numerous treatments in the hospital. Parents

often have to adjust their life habits in respect of the future of their child. The general practitioner should readily refer to social assistance aid. In addition, it is important to follow the child's overall development and to request assistance at school if required. Integrated early intervention can also provide support for the whole family. Young children can benefit from play therapy. For example, this can help to process all negative experiences they have in the hospital. Consider referring a child who is not eating well and/or has an adverse reaction to offerings of food to specialist practitioners (Speech and Language Therapists specialising in eating and/or specialised Eating Clinics/psychologists specialising in the area).

Older children may need guidance with the sense of 'feeling different', having to cope with the side effects of the drug (bad breath and body smell) and to deal with the need to take a large amount of medication at specific times. This can be very burdensome and difficult. The general practitioner is ideally placed to intervene in the various psychosocial problems in all life phases.

For males with cystinosis, the issue of fertility problems can arise. The general practitioner can actively request and offer the necessary support on a psychosocial level, as well as a referral for treatment (PESA followed by ICSI) as appropriate.

Kidney transplantation

For the general practitioner, it is important to not only focus on the kidney recipient (for example, the psychosocial aspects and the increased risk of infections or malignancies), but also on the donor of the kidney (if linked to the same general medical practice). For example, recovery after surgery can take some time. There can also be disappointment if the organ is rejected.

Patient contact/support groups

There can be a lot mutual support for those experiencing similar issues. This can be done via cystinosis or kidney patients associations. (Contact details below, see *Patient Associations*).

Consultation and referral

- **Diagnosis** The diagnosis of cystinosis preferably takes place in the Centre for Expertise in Rare Renal Diseases.
- **Treatment and guidance** The treatment preferably takes place in the Centre for Expertise in Rare Renal Diseases. Adults are seen at least once or twice a year for a check-up by an internist specialized in metabolic diseases and by a nephrologist. Children are seen at least twice to four times a year for a check-up by a paediatric nephrologist in conjunction with a paediatrician in their own region.
- See for **National centers of expertise**: www.ERKNet.org (European Reference Network for Rare Kidney Diseases).
- **Heredity** Information and advice on heredity takes place in a clinical genetic centre (via an University Medical Centre).
- **Patients' Association** provides contact and patient support.

- **Europe**
  - Cystinosis Network Europe
    www.cystinosis-europe.eu
- **Belgium**
  - AIRG Belgique
    www.airg-belgique.org
  - BOKs
    www.boks.be
- **France**
  - AIRG
    www.airg-france.fr
  - Cystinosis Foundation
    www.cystinose.fr
- **Germany**
  - Cystinose-Selbsthilfe e.V.
    www.cystinose-selbsthilfe.de
- **Ireland**
  - Cystinosis Foundation
    www.cystinosis.ie
- **Italy**
  - Associazione Cistinosi
    www.cistinosi.it
- **Netherlands**
  - Cystinose Groep Nederland
    www.cystinose.nl
- **South Africa**
  - Cystinosis Support Group
    www.cystinosis.co.za
- **Spain**
  www.grupocistinosis.org/www-airg-e.org
- **UK**
  - Cystinosis Foundation
    www.cystinosis.org.uk
- **USA**
  - Cystinosis Foundation Inc.
    www.cystinosisfoundation.org
  - Cystinosis research network
    www.cystinosis.org
  - Cystinosis research foundation
    www.natalieswish.org

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Websites

12. http://www.cystinose.nl
13. http://www.stofwisselingsziekten.nl/toon-ziekte/infantiele_cystinose/
14. http://cystinosis-europe.eu
15. http://cystinosislife.orphan-europe.com

Notes

Accountability

This brochure was created as a collaborative effort among the Dutch Cystinosis Group (CGN), the Dutch Genetic Alliance (VSOP) and the Dutch College of General Practitioners (NHG).

Dutch Cystinosis Group (CGN)
The Dutch Cystinosis Group is a diagnosis group of the umbrella organisation Adults, Children and Metabolic Diseases (VKS). The Dutch Cystinosis Group (CGN) was founded in 2000.

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Dutch Genetic Alliance (VSOP)
VSOP is the Dutch national patient umbrella organization for rare and genetic disorders with a membership of approximately 75 disease-specific patient and parent organizations. Its mission is to optimize the outcomes of biomedical and genetic research to the benefit and quality of life of patients, amongst others by stimulating and facilitating patient involvement in clinical research.
At VSOP's office in Soest, The Netherlands, approximately 25 skilled employees, most of them having an (biomedical) academic background, are active in the fields of health care policy, quality of care and patient involvement.

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The Dutch College of General Practitioners (NHG)
The Dutch College of General Practitioners is the scientific society of general practitioners. The NHG has the objective of promoting scientifically responsible professional practices by general practitioners. By translating science into general practice, the NHG contributes to the professionalism of the practitioner group. Core activities of the NHG are the development of NHG Standards and other guidelines, training and the development of products to support the general practitioner in his practice, such as patient information.

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