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La cystinose, une maladie rare métabolique héréditaire : entre traitements disponibles et besoins non satisfaits

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Par CRACAN Claude

Né le 23/09/1997 à Chisinau (Moldavie)

Le 16/05/2023

**Cystinosis, an inherited rare metabolic disease:
between available treatments and unmet needs**

**La cystinose, une maladie rare métabolique héréditaire: entre
traitements disponibles et besoins non satisfaits**

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List of acronyms

ACEi	Angiotensin-converting enzyme inhibitors
AS-OCT	Anterior Segment Optical Coherence Tomography
BSA	Body Surface Area
BVCA	Best-corrected visual acuity
CCCS	Corneal Cystine Crystal Scores
CH	Cysteamine Hydrochloride
CKD	Chronic Kidney Disease
CNE	Cystinosis Network Europe
CYS	Cysteamine (=mercaptamine)
DR	Delayed Release
EMA	European Medicines Agency
ERKNet	European Rare Kidney Disease Reference Network
ESPN	European Society for Pediatric Nephrology
ESRD	End-Stage Renal Disorder
FDA	Food and Drug Administration
HCP	Healthcare Professional
HRT	Hormone Replacement Therapy
HSCT	Hematopoietic Stem Cell Transplantation
IR	Immediate Release
IVCM	In Vivo Confocal Microscopy
Kb	Kilobase (DNA unit of length comprising 1000 nucleotide bases)
NBS	Newborn Screening
NC	Nephropathic Cystinosis
QoL	Quality of life
RPE	Retinal Pigment Epithelium
RRD	Recordati Rare Diseases (company, ex-Orphan Europe)
UBM	Ultrasound Bio-microscopy
U.K.	United Kingdom
U.S.A.	United States of America
WBC	White Blood Cell(s) (leukocytes)

Glossary

Allele: A variant of a gene, resulting from a mutation and hereditary, ensuring the same function as the initial gene but according to its own modalities. Any gene can have several alleles, which often determine the appearance of different hereditary characteristics

Autosomal: In genetics, refers to the transmission of genetic characters when these characters are carried on the non-sexual chromosomes called autosomes

CTNS: Gene encoding for cystinosis in humans

Cysteamine (=mercaptamine): Naturally present in the human body, it is a product of the degradation of cysteine. It is used in the treatment of cystinosis as a cystine-depleting agent

Cysteine: Sulfur amino acid, constituent of many proteins, which oxidizes easily in the air to cystine and plays an important role in human metabolism

Cystine: Sulfur amino acid, oxidized form of cysteine formed by two molecules of cysteine. It is an essential element for the formation of sulfur proteins such as keratin present in the structure of hair and nails. It is also present in the urine and constituent of certain bladder or kidney stones

Cystinosin: Protein of the lysosomal membrane responsible, among other things, for the transport of cystine out of the lysosomes in cells

Cystinosis: Inherited metabolic rare disease characterized by an intra-lysosomal build-up of cystine in cells

Cystinuria: Inherited metabolic disease characterized by a defect in renal tubules. It causes excessive amounts of cystine excreted in the urine. Urinary excess of cystine leads generally to the formation of cystine stones in the renal and/or urinary system, inducing kidney failure eventually. Was historically confused with cystinuria

Cytoplasm: Refers to the contents of a living cell (except the kernel) and the region between the plasma membrane and the nucleus of a cell. It includes the cytosol, the cytoskeleton and organelles

Cytosol: liquid phase in which the cytoplasmic organelles are

Enzymes: proteins found in cells that facilitate the biochemical reactions

Fanconi's syndrome: Fanconi syndrome is a rare disorder characterized by impaired renal tubular function that results in urinary excessive losses of glucose (glucosuria), bicarbonate, phosphates, uric acid, potassium, sodium and certain amino acids

Founder effect: Loss of genetic variation that occurs when a new population of a very small number of individuals is established from a larger population

Incidence: In epidemiology, the incidence of a disease is the number of new cases of that disease observed over a given period

Lysosome: Cellular organelle containing enzymes that degrade most of biological macromolecules

Newborn screening: public health initiative aimed at screening all newborns for certain rare but serious diseases, most of which are inherited

Prevalence: In epidemiology, it is the number of patients of a disease in a population at a given time, including both new and old cases

Protease: Any enzyme that breaks down the chemical bonds (peptide bonds) between amino acids to break down proteins

Recessive: In genetics, said of a gene that produces its effect only when it exists on both chromosomes of the pair (in opposition to "dominant" genes)

Preface

Why did I choose to write a thesis about cystinosis?

As a pharmacist student, fundamental sciences (cell biology, biochemistry, genetics) and pathophysiology have always interested me. But, during my internship as a strategy consultant working on projects for pharmaceutical companies, I really got started my career in the field of rare metabolic diseases. I discovered this field through galactosemia, an inherited disease caused by a deficiency of one of the enzymes involved in the metabolism of the sugar present in milk (galactose).

Luckily, the following year, I found an internship in medical affairs at the international headquarters of Recordati Rare Diseases, a medium-sized pharmaceutical company specialized in rare diseases. During this experience, I worked on several metabolic diseases, including cystinosis.

What made an impact on me is that this disease affects children who, without treatment, have serious and sometimes fatal irreversible damage. It is also the dual systemic and local damage in the patients, with various specialists (pediatricians, nephrologists, ophthalmologists, psychologists) involved, that I find stimulating. And, despite the available treatments (which is not always the case of all rare diseases), challenges remain, and the fight for these patients is far from over. While waiting for convincing results in the search for a solution that would definitively cure the patients, they lead a difficult life with cumbersome treatments to be taken for a lifetime.

Having had the chance to meet doctors specializing in this disease, representatives of patient associations, as well as the patients, this disease has left its mark on me: the commitment of professionals in response to the distress of patients' parents or patients themselves commands respect.

Having worked several months on this disease, I decided to work on this topic for my thesis subject, in order to try to give some visibility to this disease and to call out readers and students from the health world and elsewhere, to make a state of the art of the patients' care and research in this field, and to bring some lines of reflection toward the concrete and unsolved problems.

In a society where the market access, the pricing, the supply, the compliance and the observance issues towards a treatment are real challenges, I hope to make my readers curious in a field where **everyone can make a difference**. Because contributing somehow to the improvement of a patient's or a family's life is invaluable.

This is also why I wish to dedicate my professional life to a career in medical affairs applied to rare diseases, perhaps even in rare metabolic diseases, and, who knows, one day working again on cystinosis.

In order to reach out to wider audience, I decided to write my thesis in English.

I. Introduction

Rare diseases affect a relatively small number of people and therefore carry specific problems. In Europe, the commonly accepted threshold for defining a rare disease is one in 2,000 affected persons. The total number of patients worldwide is almost 400 million and increasing every year.¹

The drugs used to treat rare diseases are called "orphan drugs". These treatments are also rare, expensive, and sometimes even non-existent, leaving patients dealing with dietary restrictions and symptom treatment for instance with little hope. The research and development of new drugs for rare diseases has become one of the priorities for many international pharmaceutical companies in recent years, due to high private and public investments and funding, within a market full of opportunities with limited competition. Clinical advances have been made in treatment options with small molecule drugs, antibodies, gene therapy, stem cell therapy, etc.

Encouraging and significant improvements have also been made for the management and treatment of cystinosis, with growing visibility within the research world as shown by the increasing number of published articles about or related to cystinosis every year: 2 articles published in 1948, 68 articles published in 2022.²

Cystinosis is a metabolic rare disease characterized by an intra-lysosomal build-up of cystine in cells due to mutations in the CTNS gene which normally encodes cystinosin, a membrane transporter carrying cystine out of the lysosome.

It is inherited by autosomal recessive manner.

This impairment of cystinosin leads to accumulation of cystine, and thus cystine crystals, in every cell of the body.

One of the first organs to be affected is the kidney, usually in the first year of the patient's life. Without any treatment, the damages lead to an end-stage renal disease when the patient is 6-8 years old.

¹ https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php, accessed Oct. 2022

² <https://pubmed.ncbi.nlm.nih.gov/?term=%28cystinosis%5BTtitle%2FAbstract%5D%29&sort=date&size=200>, accessed Feb. 2023

Other tissues are also harmed (e.g. the eyes, the muscles, the central nervous system, the thyroid and the reproductive organs).

White blood cells cystine measurement is currently the most reliable technique to diagnose but also to monitor the patient in parallel of the treatment. Several treatment options exist for patients with cystinosis: cysteamine intake, dialysis, kidney transplantation, hormonal therapy; yet there is no current solution to definitively treat the patients.³

And there are still a lot of challenges and unmet needs revolving around cystinosis. Having treatment options does not necessarily mean disease progression is halted or the patients being adequately treated, not even that the patients will be benefiting from it at all.

For these reasons, it is important for pharmaceutical companies, public agencies, and even physicians to be aware of the existing issues in patients' and families' lives; I will try to present some of these with the following plan:

- Explaining what exactly is cystinosis, its background, the patients' profile, the disease impact at the physical, mental and societal levels
- Focusing on the nephropathic side of the disease
- Looking at the ocular damage in connection with the disease
- Describing the patient journey
- Summarizing the expert guidelines
- Advancing more comprehensive sources of information about cystinosis (international events and community)
- Discussing unresolved and remaining questions

Although cystinosis causes damage in all organs and tissues (kidneys and eyes, but also bone, muscles, liver endocrine system, neurological damage, digestive system, etc⁴), in this work I will describe the general aspects of the disease and focus on the renal and ocular involvement.

³ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

⁴ Ariceta et al. "Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis." Nefrologia vol. 35,3 (2015): 304-21.

II. Methodology

In order to write this thesis, I had to become familiar with the subject and its problems.

The first step consisted essentially in reading open access research articles and publications from scientific journals, filtering with keywords (e.g. nephropathic cystinosis, ocular cystinosis, cysteamine), from the most recent articles to the oldest ones. The search engine used was mainly Pubmed® (from the U.S. National Institutes of Health), with articles from the following scientific journals⁵:

Journal title	Publisher	Country	h-index ⁶
New England Journal of Medicine	Massachussetts Medical Society	U.S.A.	1079
Journal of the American Society of Nephrology	American Society of Nephrology	U.S.A.	292
Kidney international	Elsevier	U.S.A.	288
American Journal of Physiology	American Physiological Society	U.S.A	181
Orphanet journal of rare diseases	BioMed Central	U.K.	118
Pediatric nephrology	Springer	Germany	113
Molecular Genetics and Metabolism Reports	Elsevier	Netherlands	112
Cells	Multidisciplinary Digital Pub. Inst.	Switzerland	66
European Journal of Ophthalmology	Wichtig Publishing	Italy	55
Clinical kidney journal	Oxford University Press	U.K.	48
Frontiers in pediatrics	Frontiers Media	Switzerland	48

Table 1: Scientific journals containing articles used as references

⁵ Data from <https://www.scimagojr.com/> accessed Oct. 2022

⁶ The h-index is a quantitative metric based on analysis of publication data using publications and citations to provide an estimate of the importance, significance, and broad impact of a scientist's cumulative research contributions. <https://beckerguides.wustl.edu/authors/hindex>

Other sources of information are:

- GeneReviews[®]: a collection of articles published in peer-reviewed scientific journals specialized in genetic disorders.
- Orpha.net: website managed by the French National Institute of Health and Medical Research (INSERM) devoted to rare diseases and information about diagnosis, orphan drugs, clinical trials and expert networks
- Kidney.org: website of the U.S. National Kidney Foundation
- Recordati Rare Diseases' internal data

Additional sources of information were live presentations and discussions with physicians and patient associations during several events and congresses, in particular the 2022 International Cystinosis Conference, a scientific event organized by the CNE (Cystinosis Network Europe) and held once every two years.

Special mentions to Prof. Dr. Elena Levtchenko, pediatric nephrologist based in Belgium currently president of the European Society of Pediatric Nephrology, Dr. Hong Liang, ophthalmologist based in France, and Dr. Katharina Hohenfellner, pediatric nephrologist member of the German cystinosis foundation.

I had the opportunity to personally interact and ask questions to these expert physicians during quick interviews. Assisting them for some slide presentations was an honor.

III. Cystinosis: general aspects

1. History and background

Cystine was discovered and isolated in 1810 from urinary stones by W.H. Wollaston, a British chemist, who then named the substance cystic oxide. The term cystic oxide was inappropriate, as Berzelius wrote in 1833 and replaced it by cystine. But it was not until 1885 that the structure of this double amino-acid was completely elucidated by the German chemist Baumann, who named the corresponding single amino-acid cysteine, first amino-acid to be discovered. He showed that cystine is formed from the oxidation of two cysteine molecules and the formation of a disulfide bond.⁷

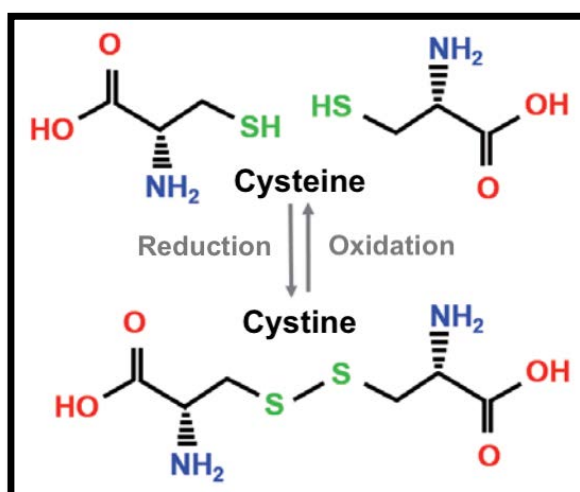


Figure 1: Cysteine and Cystine chemical structures

The first description of Cystinosis in scientific literature was in 1903 by a biochemist from Switzerland, Prof. E. Abderhalden, as a familial disease consisting in cystine accumulation. This occurred after the autopsy of a 21 months old child who could not thrive and had extremely important accumulation of cystine in several organs, especially cystine crystals in the liver and spleen.⁸

⁷ P. Avenas, *L'actualité chimique* n°450, journal of the French Chemistry Society, page n°3

⁸ Elmonem et al. "Cystinosis: a review." *Orphanet journal of rare diseases* vol. 11 47. 22 Apr. 2016

At that time and during the following years, infrequent cases of “cystine storage disorders” were reported in very young patients by clinicians. Some of these patients actually had cystinuria instead of cystinosis, but there was a confusion between these two diseases because of the lack of specific analytic methods.⁹

In 1924, Dr. G. Lignac, a pathologist from the Netherlands, provided for the first time an explicit and systematic description of cystinosis, associating the disease with its main clinical symptoms (e.g. kidney disease, growth retardation, and rickets).

The understanding of these clinical manifestations really improved in the 1930s, when three physicians from different countries, Dr. G. de Toni from Italy, Dr. G. Fanconi from Switzerland, and Dr. R. Debré from France, reported children with proteinuria, glucosuria, acidosis, and rickets. This profiled renal tubular syndrome, named Fanconi’s syndrome, is a characteristic manifestation of cystinosis. In 1952, Dr. H. Bickel associated Fanconi’s syndrome to gradual glomerular impairment in a significant cohort of patients.

The cellular and biochemical basis of cystinosis were established in 1967 by Dr. J. Schneider, an American physician, as an important milestone in the disease comprehension. With the help of new techniques precise enough to analyze and measure amino-acids levels in cells, Dr. Schneider could observe increased cystine levels in leukocytes (white blood cells) from patients’ blood samples. Subsequent studies showed that cystine was concentrated in the lysosomes of cystinosis patients’ cells.

In 1982, it was showed that this accumulation of cystine in the lysosomes was due to an impaired lysosomal export function, and eventually in 1998, during the rise of human genome sequencing, the gene encoding the lysosomal cystine carrier protein, CTNS, was identified by Town et al. on chromosome 17’s small arm (17p13.2).¹⁰

Since the 2000s, cystinosis continued to gain international attention from researchers and clinicians.

⁹ Gahl et al. “Cystinosis.” The New England journal of medicine vol. 347,2 (2002): 111-21.

¹⁰ Veys et al. “Nephropathic cystinosis: an update.” Current opinion in pediatrics vol. 29,2 (2017): 168-178.

2. Epidemiology

It is very difficult to estimate prevalence numbers considering a rare disease, this is why there will almost only be mention of estimated incidence numbers.

The overall incidence (or birth prevalence) of cystinosis is about 1 newborn patient among 100,000 to 200,000 births.¹¹

This number varies between countries, regions, and ethnical groups.

Some countries report cystinosis incidence data in its populations¹²:

Country	France	Germany	Denmark	Sweden	Australia
Incidence	1:167,000	1:179,000	1:115:000	1:260,000	1:192,000

Table 2: Reported nationwide cystinosis incidence

The disease affects 500 to 600 children in the USA with around 20 new cystinosis patients born each year.¹³

Because cystinosis is an autosomal recessive disease, consanguinity affects incidence by increasing it within some communities, creating clusters.

In some areas a founder effect leading to higher incidence was described, as for example in French Brittany region (1:26,000)¹⁴, and in the West Midlands of the United Kingdom among patients from Pakistani origin (1:3,600) which is the highest number reported so far regarding birth prevalence in cystinosis.

Other regions and ethnic groups have been reported with a founder effect and different mutations from the most common European mutation¹⁵:

- in the Amish Mennonite community in Ontario (Canada)
- in the African community of South Africa
- in other African or Middle East regions (North Africa, Egypt, Iran)

¹¹ Gahl et al. "Cystinosis." *The New England journal of medicine* vol. 347,2 (2002): 111-21.

¹² Elmonem et al. "Cystinosis: a review." *Orphanet journal of rare diseases* vol. 11 47. 22 Apr. 2016

¹³ Nesterova & Gahl (2012) *Infantile Nephropathic Cystinosis Standards of Care*, Cystinosis Research Network

¹⁴ Kalatzis et al. "Characterization of a putative founder mutation that accounts for the high incidence of cystinosis in Brittany." *Journal of the American Society of Nephrology* vol. 12,10 (2001): 2170-2174.

¹⁵ Hohenfellner et al. "NBS: Review of its Impact for Cystinosis." *Cells* vol. 11,7 1109. 25 Mar. 2022

3. Molecular basis and etiology

Genetic cause:

Cystinosis is an inherited disease caused by mutations of both alleles of the CTNS gene, found on the short arm of chromosome 17, encoding cystinosin, a lysosomal membrane transporter. As of 2017, more than 120 different mutations of the CTNS gene have been described in scientific literature.¹⁶

The most frequent mutation is a 57 kb deletion found in 3 out of 4 European cystinosis patients. While some CTNS mutations cause an absence of cystinosin or loss of its function, mutations that affect functionally unimportant regions of cystinosin account for a milder clinical course. The various CTNS mutations can explain why patients have a wide spectrum of clinical symptomatology. Individuals with infantile cystinosis carry severe mutations on both alleles. Later-onset (intermediate) cystinosis appears to be due to the inheritance of a mutation known to cause infantile disease in one allele and a relatively less clinically severe mutation in the other or due to the inheritance of a relatively less severe mutation in both alleles.¹⁷

Since the CTNS gene is mutated in cystinosis patients, the transcription and translation of this gene will lead to production of an impaired cystinosin transporter, partially or not functional at all.

¹⁶ Veys et al. "Nephropathic cystinosis: an update." *Current opinion in pediatrics* vol. 29,2 (2017): 168-178.

¹⁷ Servais et al. "Late-onset nephropathic cystinosis: clinical presentation, outcome, and genotyping." *Clinical journal of the American Society of Nephrology : CJASN* vol. 3,1 (2008): 27-35.

Cellular consequences:

In healthy cells, cystine transport occurs through the following steps¹⁸:

- ① Proteins enter in the lysosome
- ② Proteases degrade proteins into amino acids
- ③ Two molecules of the amino acid cysteine are oxidized by an enzyme (cystine reductase) to produce cystine
- ④ Cystine is then exported to the cytoplasm by a transporter: cystinosin
- ⑤ In the cytosol most cystine is readily reduced into free cysteine by cell reducing systems (mainly by the glutathione redox couple)
- ⑥ Cysteine is reused to produce new proteins

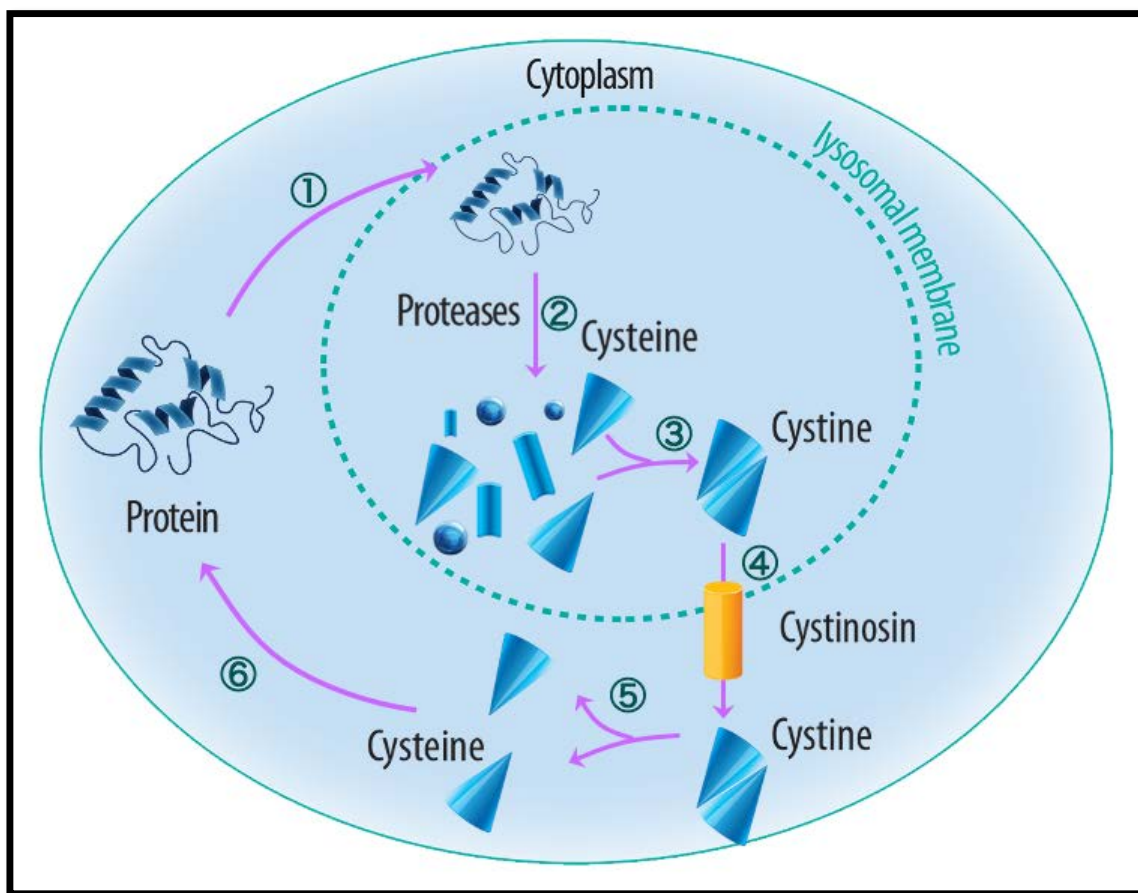


Figure 2: normal cystine transport in a healthy cell

¹⁸ Gahl et al. "Cystinosis." The New England journal of medicine vol. 347,2 (2002): 111-21.

Meanwhile in cells from patients with cystinosis, lysosomal cystine cannot be exported to the cytoplasm by cystinosin, resulting in an accumulation of cystine in the lysosome, which is poorly soluble, forming needle-shaped crystals.

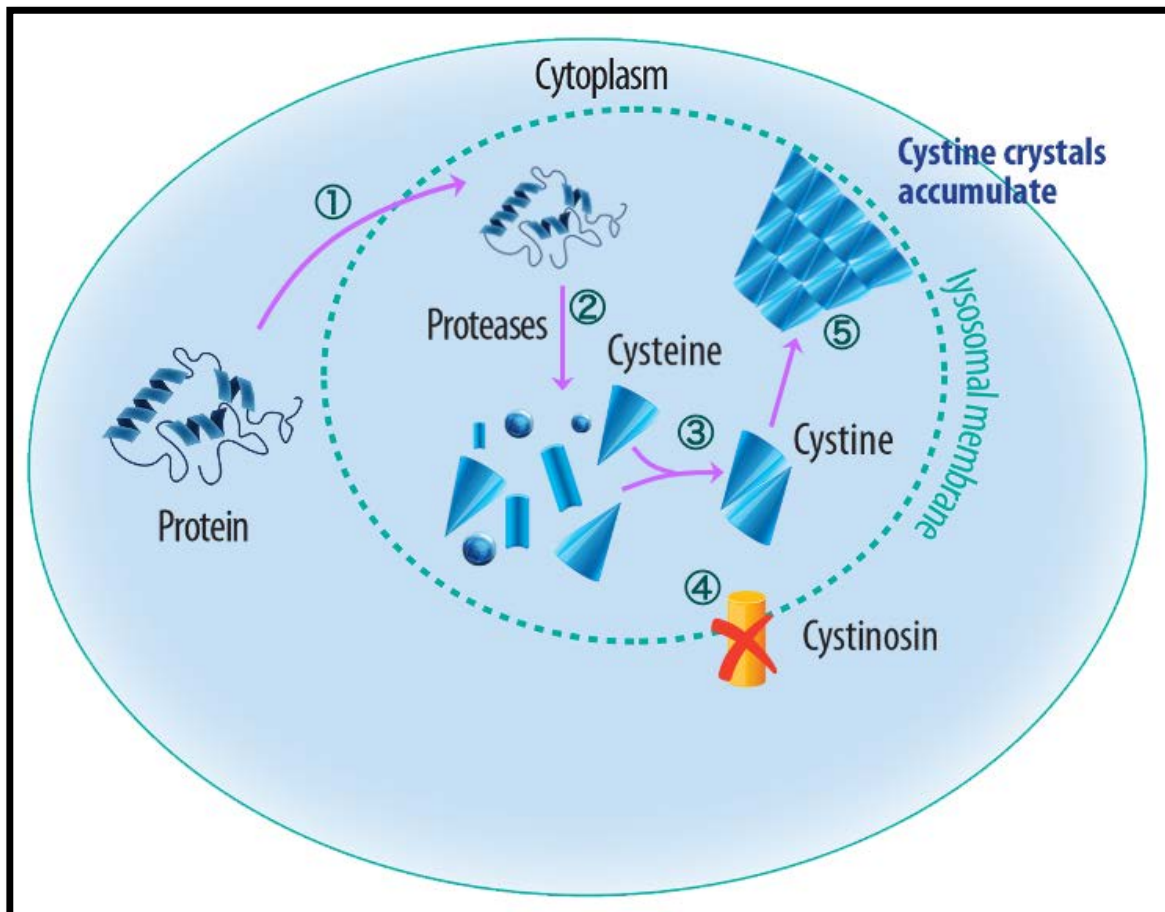


Figure 3: impaired cystine transport in a cystinosis patient's cell

The cystine crystals formed in the lysosomes will damage cells and lead to oxidative stress, mitochondrial impaired function, inflammatory response and eventually cell death. These patients suffer from accumulation of cystine crystals in almost all cells and tissues, leading to pathologic manifestations.¹⁹

¹⁹ Bäumner et al. "Nephropathic Cystinosis: Symptoms, Treatment, and Perspectives of a Systemic Disease." *Frontiers in pediatrics* vol. 6 58. 14 Mar. 2018

4. Clinical and Physio-pathology

Depending on the age at onset and the severity, cystinosis is classified into three clinical forms:^{20,21}

- Early onset / infantile nephropathic cystinosis (~95% of patients)²²
- Late onset / juvenile nephropathic cystinosis (~5% of patients)
- Adult / ocular non-nephropathic cystinosis (extremely rare)

The infantile nephropathic cystinosis form (early onset) appears from 6 to 8 months of age as renal Fanconi syndrome and is the most frequent sign.

The juvenile nephropathic cystinosis form (late onset) also presents a renal dysfunction but symptoms appear during adolescence and progress more slowly than in the infantile form.

Adult (ocular non-nephropathic) cystinosis is defined by ocular manifestations without renal disease involvement.

The accumulation of cystine crystals occurs in the cornea and the conjunctiva of the three groups of patients and is a pathognomonic characteristic of cystinosis.²³

Cystine crystal accumulation also occurs in many non-renal organs including the muscle, brain, bone marrow, liver, spleen, lymph nodes, cornea, conjunctiva, thyroid, pancreas, testes, and intestines.

Infantile nephropathic cystinosis²⁴:

Untreated infantile cystinosis presents with poor growth and proximal tubular Fanconi's syndrome at 6-12 months of age, kidney failure by the age of 10 years, and various non-renal complications including hypothyroidism and ocular disorders.

Renal tubular damage presents at the time of diagnosis and is largely irreversible.

²⁰ Shams F, et al. *Clinical Ophthalmology*. (2014); vol8: 2077-84

²¹ Servais A, et al. *Clinical Journal of American Society of Nephrology*. (2008); vol3: pp27-35

²² Emma F et al *Nephrol Dial Transplant* (2014) 29: iv87–iv94

²³ Tsilou E, et al. *Survey of Ophthalmology*. (2007); vol52: 1: p97-105

²⁴ Nesterova G & Gahl WA. *Pediatr Nephrol* 2013;28:51-59.

The profound polyuria, polydipsia, dehydration and metabolic acidosis commonly result in life-threatening hypovolemia. Failure of the proximal tubules to reabsorb phosphate and calcium leads to rickets in children; hypocalcemia sometimes results in tetany.

Other symptoms such as anorexia, vomiting, and feeding difficulties, combined with renal losses of nutrients, cause poor nutritional status and lead to failure to thrive. Cystine accumulates in virtually all organs and several complications accompany the tissue damage, including photophobia, hypothyroidism, heat prostration due to sweating impairment, and delayed puberty.

In absence of a treatment initiated early enough and maintained over time, the disease progresses and several complications occur²⁵:

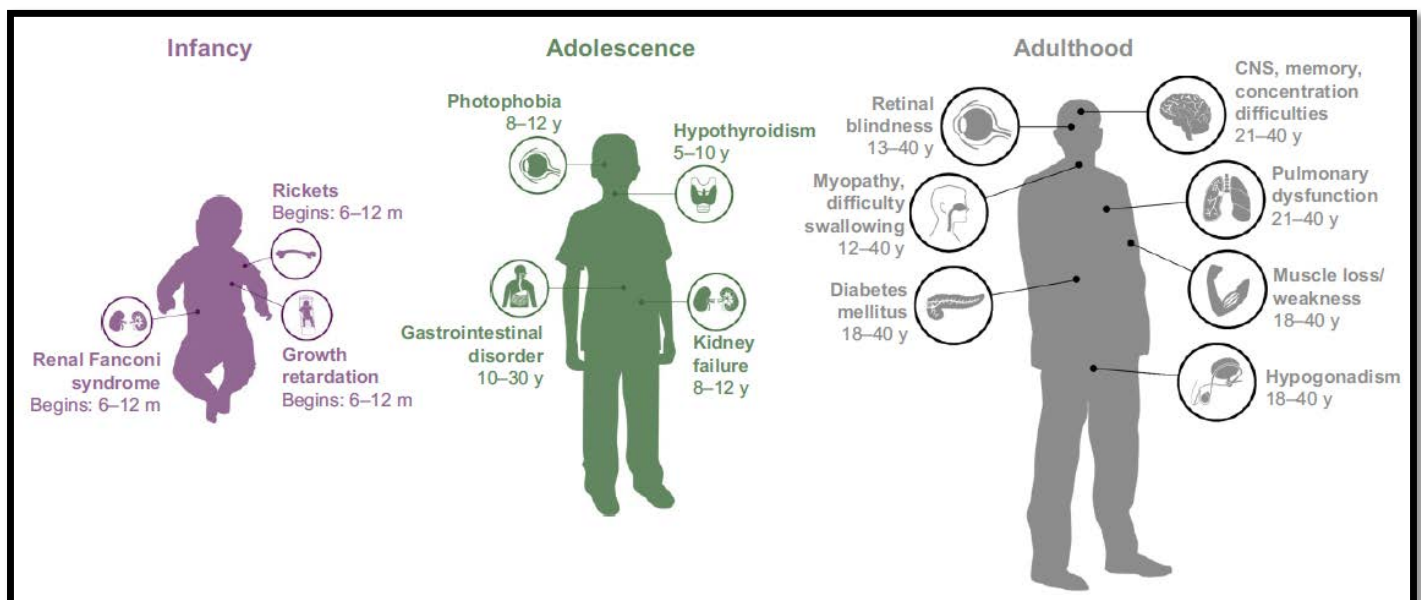


Figure 4: Schematic progression of cystinosis manifestations in absence of cystine depleting therapy initiated early enough and maintained over time

A cystine-depleting treatment, by cysteamine intake, allows patients to survive infancy and childhood, and to become adolescents and adults. Disease complications still occur in adults because of adherence problems to the treatment, therapy discontinuation, and/or late treatment initiation.

²⁵ Levchenko et al. "Expert guidance on the multidisciplinary management of cystinosis in adolescent and adult patients." Clinical kidney journal vol. 15,9 1675-1684. 15 Apr. 2022

Juvenile nephropathic cystinosis:

Late-onset (intermediate) nephropathic cystinosis is a more indolent form of the disease. The age at manifestation is later; most commonly in early adolescence (mean age at presentation: 12-13 years).²⁶

Symptoms are usually restricted to the kidneys (with a less severe form of Fanconi's syndrome and proteinuria) and eyes (photophobia).

Although complete Fanconi's syndrome often does not develop in late-onset cystinosis, renal function deteriorates as in infantile nephropathic cystinosis if untreated, and patients often experience end-stage renal failure within a few years after diagnosis (12 to 28 years).²⁷

Non-nephropathic cystinosis²⁸:

Also known as ocular cystinosis, non-nephropathic cystinosis is considered a relatively benign variant and is usually diagnosed by an ophthalmologist treating patients for photophobia. Photophobia may not begin until middle age and is not usually as debilitating as in the nephropathic form of the disease. Slit-lamp examination reveals corneal crystal deposits.

In addition to the eye, cystine crystals are present in the bone marrow and leucocytes but are absent from the kidney and the retina.

See annex for a figure describing possible disease manifestations of cystinosis.

See annex for a table summarizing age-dependent signs and symptoms.

5. Psycho-socioeconomic aspects

In addition to all of the problems generated physically by the disease and its complications or by the treatment itself (cf. side effects in "Systemic therapy, cystine-depleting treatment" part I don't see information about treatment or side effects before?), cystinosis patients face all kind of issues and difficulties psychologically, socially and economically, especially now that patients survive childhood thanks to a treatment.

²⁶ Schneider JA, et al. Ped Nephrol 1990;4:645-653

²⁷ Servais A, et al. Clin J Am Soc Nephrol 2008;3:27-35.

²⁸ Wilmer JM & Schoeber JP. Pediatr Nephrol 2011;26:205-215.

The diagnosis of a serious and life-long rare disease is a major event leading to unexpected and life-changing experience.

When a couple wants and expects a child, the future baby is often idealized and envisioned. The eventuality of a child born with a severe health disorder transforms these expectations upside down. This painful situation generates misunderstanding and struggle in the couple's life, with guilt feeling and/or imputing the illness transmission to the other parent, leading in some cases to a couple separation.

But some parents testified that managing the disease reinforced cohesiveness between all family members, with mutual support and understanding among patient's peers.

Moreover, having a child with cystinosis can put the family in a difficult financial situation because of the facts that one of the parents may have to leave his or her job in order to take care of the infant on a full-time basis.

The treatment protocol, particularly when the therapy is initiated, needs the parents to be fully committed to their child who relies on them and requires assistance, leaving aside personal plans and time, even more if they have more children.

A normal psychological structuration of the young patient is a challenge because of the difficulty to thrive and all of the time-consuming medical appointments, hospitalizations, and frequent travels to reach specialists. These also affect the patient's school attendance.²⁹

²⁹ Vaisbich et al. "Multidisciplinary approach for patients with nephropathic cystinosis: model for care in a rare and chronic renal disease." *Jornal brasileiro de nefrologia* vol. 41,1 (2019): 131-141.

The physical characteristics of cystinosis will set the patient apart from his or her classmates for example because of a short size. Studying and working may be impacted by photophobia, fatigue and absence.

The adverse effects of cysteamine (only approved treatment for cystinosis), especially the unpleasant body smell and halitosis, are badly experienced too. All of these put the patient at risk of bullying, discrimination and poor educational success, but also bad adherence to the treatment and further health complications. Despite that, some cystinosis patients have no problem making friends who are more open minded to their conditions.³⁰

Among the consequences impacting the patient and the parents, we can mention: denial, overprotection, dependence, anxiety, rejection, rebellion, lack of trust, but also positive aspects as resilience, tolerance and acceptance which are essential for going forward with treatment and life.

IV. Nephropathic Cystinosis: renal disease

1. Diagnosis

Early diagnosis' impact:

Being a rare disorder with misleading partial clinical presentation, nephropathic cystinosis (NC) is often diagnosed late while the earlier the diagnosis of this condition, the better.

This is because patient's prognosis depends on age at cysteamine treatment initiation. The sooner the patient is diagnosed, the sooner the treatment is initiated, and the better the patient will develop and avoid long term complications.

Half of patients worldwide are diagnosed with cystinosis after 12 months of age; this can be improved.³¹

³⁰ Beinart et al. "Mood and illness experiences of adults with cystinosis." Renal failure vol. 37,5 (2015): 835-9.

³¹ Emma et al. "Nephropathic cystinosis: an international consensus document." Nephrology, dialysis, transplantation - European Renal Association vol. 29 Suppl 4, Suppl 4 (2014): iv87-94.

Clinical and biochemical suspicion of cystinosis:

The rationale behind diagnosing cystinosis is a well-known clinical presentation and/or family history.

Suspicion of NC should be a reflex in all cases characterized by growth failure and Fanconi syndrome symptomatology. An archetypal patient with NC would be a dehydrated child below 12 months of age presenting polyuria, vomiting and growth failure. Analyzing the patient's serum chemistry will usually display low concentrations of potassium and sodium in the blood.³²

Even if NC is usually the leading cause to pediatric Fanconi syndrome, the physician should still consider other diseases and syndromes as a differential diagnosis. Kidney failure in children from undetermined cause can also be a sign of NC.³³

There are 3 commonly established methods to diagnose NC:

- Measuring WBC cystine level (preferential method)
- Observing the cornea during a slit lamp exam for crystals investigation
- Molecular analysis of the CTNS gene

White blood cells cystine level:

The diagnosis of cystinosis is confirmed by the amount of cystine in white blood cells. The amount of cystine is measured relative to the amount of protein in the WBC, and results are expressed as "nmol of hemicystine (or half-cystine) per mg of protein" (half-cystine is the convention used, reflecting cystine as a disulphide of cysteine). In healthy humans, mixed WBC contain less than 0.2 nmol of half-cystine per mg of protein, whereas in patients with nephropathic cystinosis the values exceed 2 nmol half-cystine per mg of protein. This sensitive technique is performed preferably in granulocytes, by High-performance liquid chromatography (HPLC) or Liquid chromatography–mass spectrometry (LC-MS).

NC can also be diagnosed before birth by testing for increased cystine in either cultured amniotic fluid cells or chorionic villi from a placenta biopsy.

³² Greenbaum "Nephropathic cystinosis: diagnosis, management, and challenges in long-term treatment." supplement to Internal Medicine News, Frontline Medical Communications, Oct. 2015

³³ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

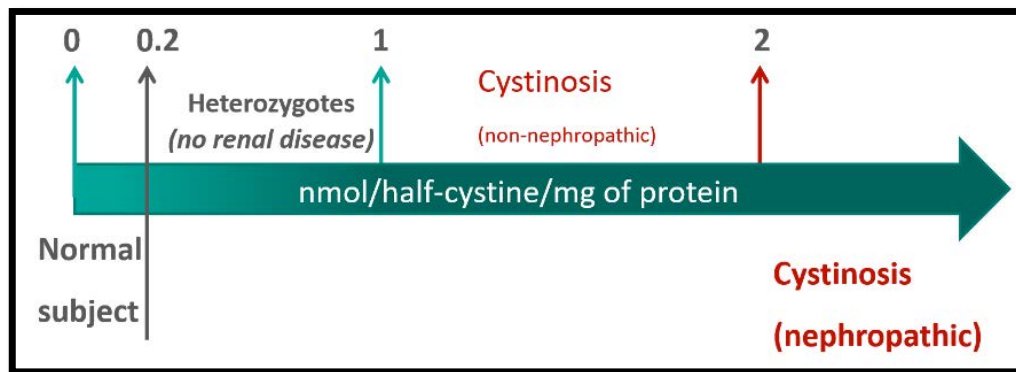


Figure 5: WBC cystine level in healthy individuals and cystinosis patients

Cystine crystals investigation:

Looking for cystine crystals in the patient's cornea during a slit lamp exam is still the most reliable, cheap and used method in developing countries. A precise assessment requires a highly trained ophthalmologist. Cystine crystals appear in the patient's cornea beginning with the 2nd year of living, meaning it is not an ideal method for very early diagnosis.³⁴

Cystine crystals can also be investigated in the bone marrow. In opposition to ophthalmic assessment it is an invasive but quite accessible method.

Molecular analysis of CTNS gene:

To detect the disease as early as possible, molecular testing of the CTNS gene is an excellent choice, but it is also time consuming and costly, so it should be performed with a valid rationale (clinical suspicion, family history). This testing reveals 95% of mutations responsible of the disease.

Newborn screening:

Currently newborn screening (NBS) is not established yet for early and systematic NC detection anywhere. However, a successful pilot study was conducted in Germany by Dr. Hohenfellner. Even if some technical barriers require maternity hospitals to adapt their NBS protocol to include NC screening, this a promising diagnosis method for developed countries where pathogenic variants are known.³⁵

³⁴ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

³⁵ Veys et al. "Nephropathic cystinosis: an update." Current opinion in pediatrics vol. 29,2 (2017): 168-178.

2. Symptoms and evolution

Kidneys are the most important organs damaged by cystinosis and are early target of the disease which leads to death if the patient is left untreated.

Renal symptomatology includes Fanconi syndrome, impaired glomerular function and eventually End-Stage Renal Disorder (ESRD).³⁶

Proximal tubular dysfunction leads to Fanconi syndrome at around 6-12 months of age; it is defined by leakage in the urine of amino-acids, potassium, magnesium, sodium, phosphates, bicarbonates, calcium, glucose, carnitine and other proteins. Consequently, imbalance of these occurs frequently in bloodstream.

These metabolic defects lead to growth retardation or failure leaving the patient shorter than healthy children, rickets, excessive urine elimination, and vomiting leading to dehydration.

In absence of cystine depleting therapy, ESRD occurs in patients around 8-10 years old.

For patients with juvenile cystinosis, these symptoms are less severe and inching down.

For patients with adult (non nephropathic) cystinosis, kidneys and other organs (except from the eyes) are not damaged.

See annex for a figure describing possible disease manifestations of cystinosis.

See annex for a table summarizing age-dependent signs and symptoms.

3. Symptomatic and systemic treatments

See annex for an overview of treatments of nephropathic cystinosis.

Symptomatic therapies:

Cystinosis patients have supportive treatments, which do not target the cause of the disease but help relieve its symptoms. Feeding and treatment administration in children can be done with the help of a naso-gastric tube if needed.

³⁶ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

Electrolyte compensation therapy is usually prescribed to the patient as per os solutions with sodium, potassium, bicarbonate, phosphate, vitamin D. This supplementation has to be closely monitored and adjusted consequently in order to avoid complications.

Indomethacin is often prescribed for cystinosis patients to improve sodium reabsorption but there is no recommendation so far for this use, thus it still has to be justified.

Dietary recommendations are important, especially a high caloric regimen.

Hormone replacement therapy (HRT) is used to treat several endocrine dysfunctions: hypothyroidism, pancreatic function, growth retardation, low testosterone level.

Deterioration of glomerular and renal functions can be slowed down by therapy with Angiotensin-converting enzyme inhibitors (ACEi), with close monitoring to avoid hypotension. Combination with indomethacin is strictly forbidden.

In patients suffering from kidney failure, dialysis followed by renal transplantation are performed. The latter dramatically improved patients' survival, solving the bad or absent kidney function only, with systemic cysteamine treatment remaining very important in transplanted patients too. Cystine crystals can be found in the kidney graft but they are due to crystals present in some leukocytes from the host and do not significantly damage the graft.

Obviously, transplanted cystinosis patients' immune function is controlled with immunosuppressors and monitored to avoid graft rejection.³⁷

Systemic therapy, cystine-depleting treatment:

Cysteamine, a simple aminothiols also called mercaptamine, is the only cystinosis specific drug currently marketed. It is a small molecule capable of depleting cystine in cells' lysosomes. It is administered orally as cysteamine bitartrate.

³⁷ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

Cysteamine's mechanism of action is summarized as follow:

- ① Cysteamine can freely enter the lysosome
- ② It interacts with cystine to produce cysteamine-cysteine, a disulfide complex
- ③ This complex is transported out of the lysosome by the lysine transporter.

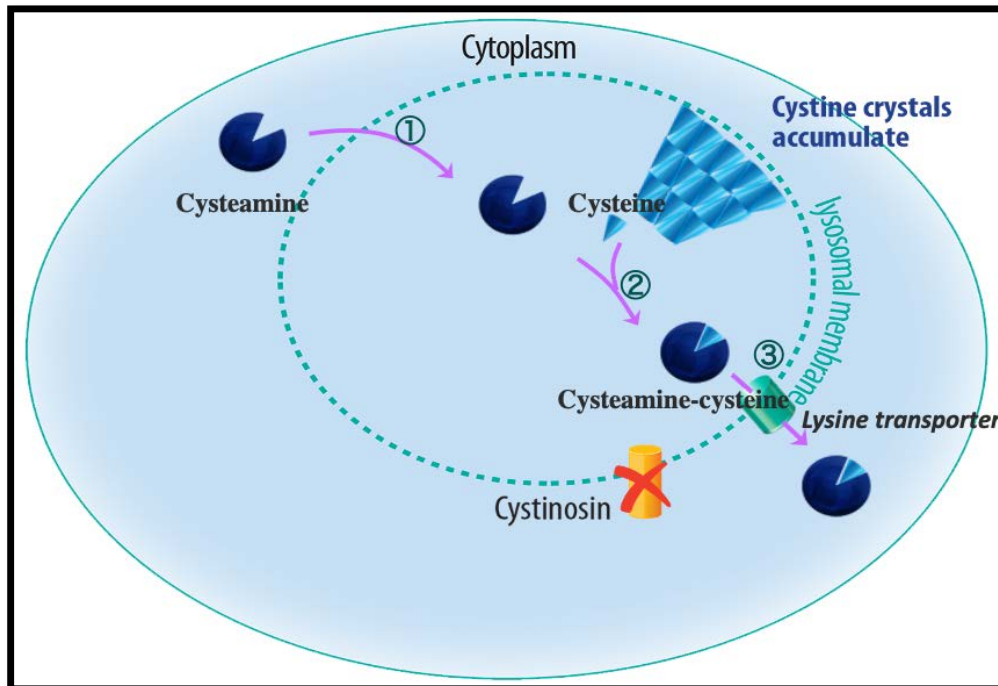


Figure 6: Cysteamine mechanism of action in the cell

The drug exists as immediate-release cysteamine (IR-CYS) marketed by Mylan in the USA (1994) and by Recordati Rare Diseases (1997) in most of other countries (Cystagon®). More recently a delayed-release form of cysteamine (DR-CYS) capsules was marketed by Raptor Pharma (2013, Procysbi®).³⁸

Likewise kidney transplantation, cysteamine revolutionized patients' prognosis and survival. When taken early enough, it has been proven to postpone ESRD, and logically kidney transplantation, by up to 10 years. It also delays occurrence of extra renal manifestations (hypothyroidism, myopathy, pulmonary damage, pancreatic damage, failure to thrive). Ideally, cysteamine should be started in the first year of age, and continued lifelong without interruption with good observance in order to keep WBC cystine levels under 1 nmol of hemi-cystine per mg of proteins. Yet, cysteamine is useless against Fanconi syndrome and corneal crystals build-up.

³⁸ Elmonem et al. "Cystinosis: a review." Orphanet journal of rare diseases vol. 11 47. 22 Apr. 2016

To maintain satisfying and low cystine levels, IR-CYS capsules have to be taken every 6 hours i.e. 4 times per day.

In order to prevent toxicity, dosage of cysteamine in patients below 12 years of age is calculated with patient's body surface area (BSA)*: 1.30 grams of cysteamine per square meter of BSA per day. For patients above 12 years of age, weighing at least 50 kg, recommended dosage is 2 grams per day of cysteamine. Dosage should not exceed 1,95 g/m²/day.³⁹

Regarding adverse effects of cysteamine, patients frequently reported transient gastro-intestinal events such a vomiting, nausea, stomach pain, and fatigue, allergic rash, seizures. These adverse reactions can be prevented or reduced by progressive dosage increase, starting from a small dose.

Metabolization of the drug also leads to production of organosulfur molecules responsible of unpleasant breath odor (halitosis) and body odor. In answer to these, patients can try vitamin B2 supplementation and chlorophyll-based products to reduce or mask bad smell.

Clinical trials for cysteamine did not include pregnant women, but preclinical results showed teratogenicity in rats, so cysteamine therapy should be discontinued in female patients confirmed to be pregnant as a precaution.⁴⁰

Interestingly, in the past 12 months cysteamine was the main topic of 4 published scientific articles as a potential treatment against Covid-19 viruses (SARS-CoV-2). It showed in vitro antiviral function against several variants, and could be a good preventive or supportive therapy if further trials are conducted in humans this time.^{41,42,43,44}

* BSA = $[(4 \times W) + 7] / (W + 90)$ with W being weight in kg, formula for pediatric population

³⁹ www.ema.europa.eu/en/documents/product-information/cystagon-epar-product-information_en.pdf

⁴⁰ Beckman et al. "Developmental toxicity of cysteamine in the rat" *Teratology* vol. 58,3-4 (1998): 96-102.

⁴¹ Khanna et al. "Thiol drugs decrease SARS-CoV-2 lung injury in vivo and disrupt SARS-CoV-2 spike complex binding to ACE2 in vitro." *bioRxiv : the preprint server for biology* 2020.12.08.415505. 11 Nov. 2021

⁴² Alonzi et al. "Cysteamine with In Vitro Antiviral Activity and Immunomodulatory Effects Has the Potential to Be a Repurposing Drug Candidate for COVID-19 Therapy." *Cells* vol. 11,1 52. 24 Dec. 2021

⁴³ Alonzi et al. "Cysteamine exerts in vitro antiviral activity against the SARS-CoV-2 Delta and Omicron variants." *Cell death discovery* vol. 8,1 288. 15 Jun. 2022

⁴⁴ Thoene et al. "In vitro activity of cysteamine against SARS-CoV-2 variants." *Molecular genetics and metabolism* vol. 137,1-2 (2022): 192-200.

4. Monitoring

A close general patient follow-up is essential. Recurring examination has to be implemented in children with Fanconi syndrome (at least 4 times a year) to evaluate growth evolution, metabolic levels and WBCs cystine. Cysteamine dosage will be modulated accordingly. In the case of renal transplantation, patients will be monitored following the hospital protocols. Since extra-renal complications can appear and develop, patients and physicians should look after any new and unexpected events and annual check-ups by specialist physicians in several areas (endocrinology, ophthalmology, neurology) are needed. Neuro-cognitive testing should be performed before primary and secondary school. Psychological monitoring is also frequently useful to help patients deal with social, academic and professional issues.⁴⁵

Cystine in WBCs is currently the single biomarker to monitor efficacy of cysteamine and patient's observance. It is not as specific as a monitoring method could be ideally; the perfect method would be a cystine level evaluation directly in the lysosomes of the cells. But such method would be too invasive, particularly if we consider infants. WBC cystine levels should be preferably measured in polymorphonuclear leukocytes rather than in mixed leukocytes since cystine accumulation is higher in these compared to lymphocytes or other white blood cells.⁴⁶ WBC cystine levels should be measured at the very least once a year (for controlled patients).

See annex for an overview of the recommended follow-up in NC patients.

5. Issues and unmet needs

Patients, families and physicians face many problems, leaving just as many unmet needs.

Below are some examples related to the context of scientific research about cystinosis but also connected to the daily reality of patients' lives.

⁴⁵ Wilmer et al. "Cystinosis: practical tools for diagnosis and treatment." *Pediatric nephrology* vol. 26,2 (2011): 205-15.

⁴⁶ Elmonem et al. "Cystinosis: a review." *Orphanet journal of rare diseases* vol. 11 47. 22 Apr. 2016

The first problem is adherence in patients which depends on many factors, like patient education and age.

In 2015, Ariceta et al. published an article about adherence in cystinosis patients, and showed that, in the patients they followed, adherence was good in children below 11 but was progressively declining above this age and after puberty. This can be explained by adolescents being more autonomous than infants, patients not being motivated to be treated anymore, and transitioning issues when follow-up changes from pediatric to adult medical care.⁴⁷

The cysteamine treatment regimen weighs a lot on the patient's life: IR-CYS it has to be taken every 6 hours in the form of many capsules, as a life-long treatment. This means, strictly following this regimen, the patient won't sleep more than 6 continued hours and won't ever have a satisfying sleep time duration.⁴⁸

Adverse events of cysteamine therapy are usually mild and transient, but halitosis and body smell are to be taken seriously into consideration since it is one the frequent cause of bad treatment adherence because of bullying at school for instance.

In response to the search of better efficacy and improved quality of life, a novel cysteamine formulation, characterized by a delayed release of the drug in the digestive tract and a twice daily administration, was developed by Raptor Pharmaceuticals (now Horizon Therapeutics) and approved by the FDA and EMA in 2013.

The rationale behind its conception was that cysteamine absorption in the small intestine results in higher cysteamine concentration in blood compared to stomach absorption.

Although DR-CYS has been proven to improve compliance thanks to its more convenient dosing regimen, WBC cystine levels are higher in patients treated with DR-CYS than in those with IR-CYS on a 12 hours period of time, and DR-CYS is still hard to access because of it being 5 to 25 times more expensive than IR-.

⁴⁷ Ariceta et al. "Cysteamine adherence in patients with cystinosis in Spain: successful in children and a challenge in adolescents and adults." *Nephrology, dialysis, transplantation* vol. 30,3 (2015): 475-80.

⁴⁸ Hirshkowitz et al. "National Sleep Foundation's sleep time duration recommendations: methodology and results summary." *Sleep health* vol. 1,1 (2015): 40-43.

This issue brought specialists to recommend higher dosage for DR-CYS with a 3 times daily intake (every 8 hours) instead of 2 times daily.⁴⁹

With patients being transplanted and treated, overall survival led them to reach age to conceive and raise children. Since cysteamine should be stopped in pregnant patients as a precaution during the entire pregnancy, it is an important decision for the patient which should be carefully considered.⁵⁰

Considering the cystine monitoring method, the large blood sample required to perform the technique, cystine instability, the non-availability of the method in developing countries are all issues that make WBC cystine level measure imperfect.

When patients reach adolescence, transitioning from specialist and family care to adult and self-managed care is a difficult process with high risk of non-compliance to the treatment, missed medical visits and other potentially leading to severe complications such as graft loss.⁵¹

Other more practical issues occur depending on the drug companies. For example, patients complain from bottle caps too tight which they cannot unscrew themselves to access the pills due to reduced muscular capacities in cystinosis patients. Also, supply, pricing, reimbursement problems can sometimes deprive entire countries from the drug.⁵² It is up to the industrial pharmaceutical companies to properly provide their product and to adapt manufacturing and logistics processes when needed because patients and physicians rely on them.

⁴⁹ van Stein et al. "A comparison of immediate release and delayed release cysteamine in 17 patients with nephropathic cystinosis." *Orphanet journal of rare diseases* vol. 16,1 387. 14 Sep. 2021

⁵⁰ Elmonem et al. "Cystinosis: a review." *Orphanet journal of rare diseases* vol. 11 47. 22 Apr. 2016

⁵¹ Raina et al. "Structured Transition Protocol for Children with Cystinosis." *Frontiers in pediatrics* vol. 5 191. 31 Aug. 2017

⁵² Bertholet-Thomas et al. "Worldwide view of nephropathic cystinosis: results from a survey from 30 countries." *BMC nephrology* vol. 18,1 210. 3 Jul. 2017

Patients are always eager for innovative solutions and treatments, better self-care information, established transitioning protocol, multi-disciplinary expert guidance and recommendations in order to partially alleviate their burden and to have a better quality of life.

6. How to improve patients' QoL

There are many possible ways to improve cystinosis patients' clinical profile and quality of life, here are some examples.

Companies and researchers are working on new and innovative therapies, hoping someday to be able to find a curative solution that would definitively treat the patient without the need for a life-long treatment.

In the meantime, patients and physicians have to deal with current therapeutic solutions and drugs and adapt the treatment regimen in order to have a good effectiveness/compliance balance. Some physicians suggest for example to mix IR-CYS and DR-CYS within a treatment regimen, by administrating two doses of IR-CYS during the day (one at 8 a.m., one at 2 p.m.) then one dose of DR-CYS in the evening (at 8 p.m.). This hybrid regimen could be a good compromise.

Cystine-depleting therapy should be initiated earlier than what happens in common practice. In 2022, Hohenfellner et al. conducted a study reinforcing previously published data regarding how good adherence with cysteamine treatment is linked to better conservation of kidney function, and regarding how precocious cysteamine therapy implementation (before 2 months of age) could prevent renal replacement therapy, meaning in patients treated within the second year of life or later, renal damage is already quite advanced, hence the high benefit of newborn screening for precocious diagnosis of the disease.⁵³ In a subsequent publication, experts claimed that clinical outcomes in patients suffering from NC do not depend on genotype, but on age at treatment initiation, strengthening once again the rationale for newborn screening introduction.⁵⁴

⁵³ Hohenfellner et al. "Beneficial effects of starting oral cysteamine treatment in the first 2 months of life" *Molecular genetics and metabolism* vol. 136,4 (2022): 282-288.

⁵⁴ Veys et al. "Outcome of infantile NC depends on early intervention, not genotype: A multicenter sibling cohort study." *Journal of inherited metabolic disease*, 10.1002/jimd.12562. 18 Sep. 2022

NBS programs are very effective to diagnose newborns affected by rare and severe diseases in order to treat them as early as possible. Developed countries usually rely on NBS to diagnose more or less numerous specifically targeted diseases, with great variation between nations' programs, in order to decrease mortality in their population. Some experts have high expectations regarding the ability of NBS to radically change cystinosis management and prognosis. Since there are above 150 different CTNS mutations mentioned in scientific literature, countries which include cystinosis in their NBS program should target the specific mutations most represented in their population. Barriers to the implementation of a NBS program targeting also cystinosis are: the cost to implement such systematic screening in developing countries, and the absence of reported CTNS mutations and founder effect.⁵⁵

From physician's side, better patient education and multidisciplinary guidance could also contribute to better patient care.

Pharmaceutical companies should put more efforts into suitable drug formulation and packaging (for example it is difficult to administer oral capsules to infants), and could develop more digital tools and content to help cystinosis patients to be proactive and manage their health.

7. Research pipeline and ongoing studies

The prognosis of patients with cystinosis has surely improved a lot thanks to cysteamine therapy, but it is still not enough since cystine-depleting therapy is not curative: it only bypasses the impaired lysosomal cystine transport, thus retarding complications like ESRD but not solving them. Furthermore, dysfunctional cystinosis is also linked to other cellular mechanisms being impaired (associated with Fanconi syndrome) that are not affected in any way by cystine-depleting therapy.⁵⁶

There are several innovative approaches under investigation in humans:

⁵⁵ Hohenfellner et al. "NBS: Review of its Impact for Cystinosis." *Cells* vol. 11,7 1109. 25 Mar. 2022

⁵⁶ Bäumner et al. "Nephropathic Cystinosis: Symptoms, Treatment, and Perspectives of a Systemic Disease." *Frontiers in pediatrics* vol. 6 58. 14 Mar. 2018

- Tolerance induction through chimerism with hematopoietic stem cell transplantation (HSCT) before kidney transplant
- Hematopoietic stem cell (HSC) gene therapy
- CTNS mRNA therapy
- Non-sense mutation readthrough via ribosome modulation

Hematopoietic Stem Cell Transplantation:

Kidney transplantation is the most effective solution against ESRD.

Despite improvements in immunosuppressive therapies, long term graft survival is still a problem with only one in two patients surviving 10 years post-transplantation because of drug toxicity and rejection problems. Ongoing research in the field of cell therapies brings hope for sustainable organ transplantation without need of life-long immunosuppressor treatment by the means of tolerance induction. Cell therapies achieving immune tolerance via mixed chimerism (defined by a mix of hematopoietic stem cells from both host and donor origin) have been successfully tested in several animal species and models. This technology is currently investigated in human trials. Applicability and advantages of HSCT have been proved, and further encouraging results are expected. If applied in cystinosis, QoL of patients in need of kidney transplant would be hugely improved although the disease would not be cured.^{57,58,59}

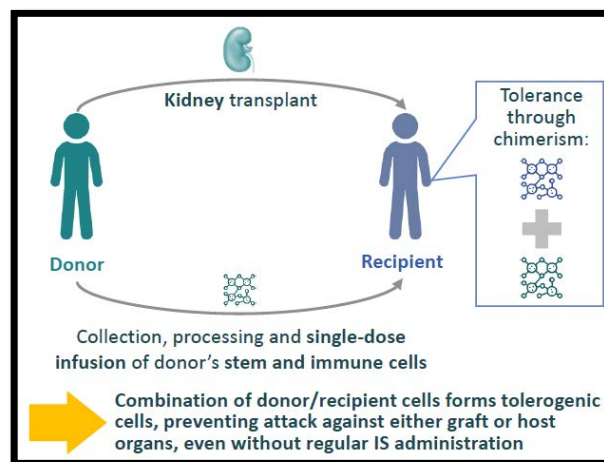


Figure 7: Chimerism therapy creates tolerance by injecting donor cells into recipient's body (simplified mechanism)

⁵⁷ Chhabra et al. "HSCT-Based Approaches for Tolerance Induction in Renal Transplant." *Transplantation* vol. 101,11 (2017): 2682-2690.

⁵⁸ Spitzer et al. "Transplantation Tolerance through Hematopoietic Chimerism." *The New England journal of medicine* vol. 386,24 (2022): 2332-2333.

⁵⁹ <https://www.medeortx.com/our-focus.php>

Hematopoietic stem cell (HSC) gene therapy:

Gene therapy is a promising approach for treating genetic disorders like cystinosis. The goal of gene therapy is to introduce a functional copy of the faulty gene into the patient's cells, thereby correcting the underlying genetic defect.

In cystinosis patients, cystinosin expression is impaired in all cells of the body. Autologous (meaning donor and receiver are the same individual) HSC gene therapy is investigated as a solution in order to restore correct CTNS genes in all cells. Autologous HSC gene therapy is substantially safer than allogeneic HSC transplantation because it prevents the risk of Graft-versus-Host-Disease and immune rejection, and it does not require any immunosuppressive treatment. The patients' own stem cells are modified ex-vivo to correct the gene impairment and then transplanted back to the same patient. Patients still require a moderate myeloablation conditioning during the process. Safety risks in this technique reside in the use of retroviral carriers to bring the healthy gene copy within the genome of the patients' cells.

The mechanism of action of this therapy consists in the transplanted gene-edited HSCs differentiating into macrophages that will transfer "healthy" lysosomes (having functional cystinosin) to the adjacent endogenous host cells via nanotubes. In return, impaired cells will use the same tunnels to transfer cystine-loaded lysosomes to the mentioned macrophages, thus establishing a bidirectional correction mechanism.

All tissues will benefit from this bidirectional exchange, leading to a significant decrease of cystine levels.⁶⁰

⁶⁰ Cherqui "Hematopoietic Stem Cell Gene Therapy for Cystinosis: From Bench-to-Bedside." Cells vol. 10,12 3273. 23 Nov. 2021

Mechanisms of action

Macrophages with CTNS transgene restore cystine recycling to CTNS^{-ve} cells via:

1. Exosomes / Microvesicles – transfer of cystinosin, CTNS mRNA
2. Tunneling nanotubes – transfer of corrected lysosomes, cystinosin, CTNS mRNA

Net result: Corrected lysosomes in cells

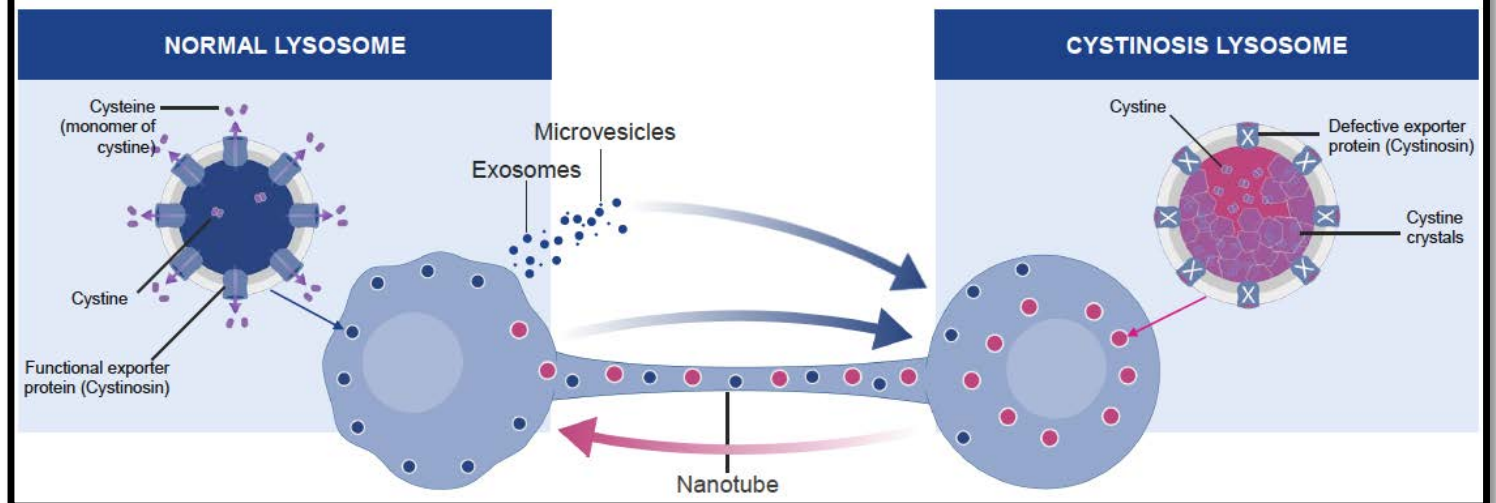


Figure 8: Genetically modified macrophages restore normal cystine recycling

Genetically modified HSC have been successfully used in mice with good efficacy and safety, opening the way to the phase I/II started in 2019 and currently ongoing as a collaborator-sponsored clinical study of AVR-RD-04 (from Avrobio Inc.) in humans. The trial is conducted at the University of California San Diego and funded partially by the Californian Institute for Regenerative Medicine, the U.S. National Institute of Health and the Cystinosis Research Foundation.

If results from this trial are satisfying regarding effectiveness and safety, cystinosis patients could be cured for the rest of their life thanks to a single HSC transplantation. Still, there is a long path before reaching this achievement, with many clinical, toxicology, economical, regulatory and production challenges.⁶¹

⁶¹ Cherqui "Hematopoietic Stem Cell Gene Therapy for Cystinosis: From Bench-to-Bedside." Cells vol. 10,12 3273. 23 Nov. 2021

Figure 8: from Avrobio's 2022 Cystinosis program update: <https://investors.avrobio.com/static-files/1ac19441-6507-49d9-bb3e-ed0900e01c1c>

CTNS mRNA therapy:

Messenger RNA (mRNA) therapy for cystinosis is an innovative approach that involves the use of synthetic mRNA introduced into patient's cells to produce functional cystinosin transporter.

The use of such therapy has several advantages, including rapid expression of the protein after introduction of the mRNA into the host body and the fact that it does not involve permanent changes to the genome.

Expression of cystinosin through this method is transient; this could be considered as a disadvantage because it would imply the need of repeated and long-term administration but is also offers dosing flexibility and controlled safety. Regarding the latter, immunogenicity of mRNA can be a concern in humans, so future studies will have to take it into consideration.

While mRNA therapy for cystinosis is still in the early stages of development, it has shown promising results with decrease of cystine levels in a recent preclinical and in vitro study performed by a research team from the Katholieke Universiteit in Leuven (Belgium) and may provide an effective treatment option for cystinosis.

Next steps in the development of mRNA therapy in cystinosis include targeting kidney cells in cystinosis rodent models and developing of a kidney-targeting delivery vehicle for mRNA.

Considering the immense interest in mRNA-based therapies, especially since the COVID-19 pandemic, there is a good chance that a pharmaceutical company will look at this therapeutic opportunity in cystinosis to continue its development in future clinical setups, at least I hope so.⁶²

⁶² Bondue et al. "CTNS mRNA as a potential treatment for nephropathic cystinosis" bioRxiv 2023.04.28.538106, pre-print; <https://doi.org/10.1101/2023.04.28.5381>

Non-sense mutation (premature stop codon) readthrough:

Translation of mRNA to proteins in cells is done by ribosomes. Modulating ribosomes is a research opportunity to address many diseases.

About 15% of cystinosis patients worldwide carry one or more nonsense mutations that halt translation of the CTNS protein. There is ongoing research investigating the use of non-sense mutation read-through techniques as a potential therapy for cystinosis.

Stop codons are a natural part of our genetic code and are essential for the proper functioning of protein synthesis. They act as a signal for the ribosome to stop translating mRNA and release the newly synthesized protein. Stop codons are not inherently noxious or harmful, but mutations that create premature stop codons can result in the production of truncated, non-functional proteins.

Read-through therapy involves the use of small molecules that can promote the translation of the non-functional protein into a full-length functional protein.

ELX-02 is an experimental aminoglycoside analog molecule developed by Eloxx Pharmaceuticals to bypass nonsense mutations causing disorders. Orally bioavailable, it can be taken as a pill. It works by binding to the ribosome and promoting the incorporation of an amino acid at the site of the premature stop codon to allow the ribosome to « read » through nonsense mutations, carrying protein translation to the end. This way, fully functional proteins are generated. In cystinosis patients, it would allow to produce functional cystinosin when the CTNS gene mutation responsible of the disease is a nonsense mutation.⁶³

Off-target effects can occur when a drug promotes the read-through of non-natural stop codons, leading to the production of aberrant proteins. This could potentially result in unwanted side effects or toxicity.

ELX-02 is a small molecule designed to selectively promote the translation of the non-functional cystinosis protein, without affecting the translation of other proteins. Therefore, the therapy is intended to be highly specific and to avoid off-target effects.

⁶³ Kerem “ELX-02: an investigational read-through agent for the treatment of nonsense mutation-related genetic disease.” Expert opinion on investigational drugs vol. 29,12 (2020): 1347-1354.

After successful preclinical and phase I trials showing promising safety and efficacy, a phase II trial was started in 2019 but was discontinued. This decision was based on an interim analysis of the data, which showed that the trial was unlikely to meet its primary endpoint: demonstrate a statistically significant reduction in cysteamine levels with ELX-02 treatment compared to placebo.^{64, 65} While the discontinuation of the trial is disappointing, it does not necessarily mean that the therapy is not effective or that other non-sense mutation read-through therapies will not be successful in the future.

As a matter of fact, another aminoglycoside, geneticin, was demonstrated by a research team from McGill University (Montréal, Canada) to induce translational read-through of premature stop codon in the CTNS gene of cells extracted from cystinosis patients, generating sufficient functional cystinosin to reduce pathologic cystine accumulation in these cells.⁶⁶

Overall, there is hope for patients with cystinosis that a non-sense mutation read-through therapy could be an effective treatment option. However, it is important to note that further research is needed to fully evaluate safety and efficacy.

⁶⁴ "A Phase 2 Study of ELX-02 in Patients With Nephropathic Cystinosis" ClinicalTrials.gov NCT04069260

⁶⁵ <https://investors.eloxxpharma.com/news-releases/news-release-details/eloxx-pharmaceuticals-reports-fourth-quarter-and-full-year-2019>

⁶⁶ Brasell et al. "The aminoglycoside geneticin permits translational readthrough of the CTNS W138X nonsense mutation in fibroblasts from patients with NC." Pediatric nephrology (Germany) vol. 34,5 (2019): 873-881.

V. Ocular Cystinosis: local disease

1. Diagnosis

Initially, the patient is diagnosed with cystinosis by pediatric nephrologists in case of failure to thrive and Fanconi syndrome. Since cystine crystals will appear in any case (around 1 year of age), the patient should be next quickly referred to an ophthalmologist who will perform an ophthalmic examination. This assessment consists in evaluating ocular cystinosis symptoms, typically: photophobia, visual disruption, eye discomfort and tearing.

Concretely, the patient undergoes visual acuity tests, a self- and clinician-assessed photophobia evaluation, a slit lamp exam for crystal detection (especially in cornea) and intra-ocular pressure measurement.

The oldest scoring method used for assessing cystine crystal deposition in the eye is the **corneal cystine crystal score (CCCS)**, created by Prof. Gahl and his colleagues in 2000. This is a subjective evaluation of the degree of cystine deposition in the cornea, typically performed by an ophthalmologist using a slit-lamp. The CCCS ranges from 0 to 3 based on the comparison with a library of slit-lamp photographs of corneas established by Prof. Gahl, with 0 indicating no visible crystals and 3 indicating the presence of numerous large crystals.^{67, 68, 69}

The CCCS is just one measure of the severity of cystinosis-related eye disease, and it is typically used in conjunction with other measures such as visual acuity and measures of eye structure and function. Generally, the higher the corneal cystine crystal score, the greater the degree of visual impairment and the more severe the disease. However, the relationship between cystine crystal deposition and visual function is complex and varies between patients, so the score should be interpreted in the context of other clinical findings and patient symptoms.

⁶⁷ Gahl et al. "Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops." *Molecular genetics and metabolism* vol. 71,1-2 (2000): 100-20

⁶⁸ Pinxten et al. "Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis." *Ophthalmology and therapy* vol. 6,1 (2017): 93-104.

⁶⁹ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: A Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthal. and therapy* vol. 7,2 (2018): 307-322

Best-corrected visual acuity (BCVA) is another important measure of visual function that is typically evaluated in cystinosis patients. This test involves measuring the patient's ability to see clearly, with corrective lenses if needed.

The patient is asked to identify letters or symbols of different sizes on an eye chart, such as the Snellen chart, from a standard distance (6 meters). The patient's ability to correctly identify the smallest letters or symbols determines their BCVA score. The results are reported as a fraction (or decimal) where the numerator is the testing distance (6 meters) and the denominator the distance at which a patient with normal vision can identify the respective letter.

A value of 6/6 (or 1.0) represents normal visual acuity.

Example: A letter from the 6/12 line of the eye chart would be able to be seen by a patient with normal (6/6) vision at a testing distance of 12 meters, but for a patient with reduced vision (e.g. 6/12) the letter would need to be moved closer (to 6 meters) in order to be seen.

In cystinosis, BCVA can be affected by several factors, including corneal crystal deposition, glaucoma, and retinopathy.

BCVA is used to monitor the progression of cystinosis-related eye disease over time and to assess the effectiveness of treatments aimed at improving visual function. However, it is important to note that BCVA is only one aspect of visual function and may not fully capture the impact of cystinosis on a patient's quality of life.⁷⁰

Together, these visual tests provide important information on the presence and severity of cystine crystal deposition in the eye and the overall visual function of the patient. They are important tools for monitoring disease progression and assessing the effectiveness of treatments for cystinosis-related eye problems.

⁷⁰ Pinxten et al. "Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis." *Ophthalmology and therapy* vol. 6,1 (2017): 93-104.

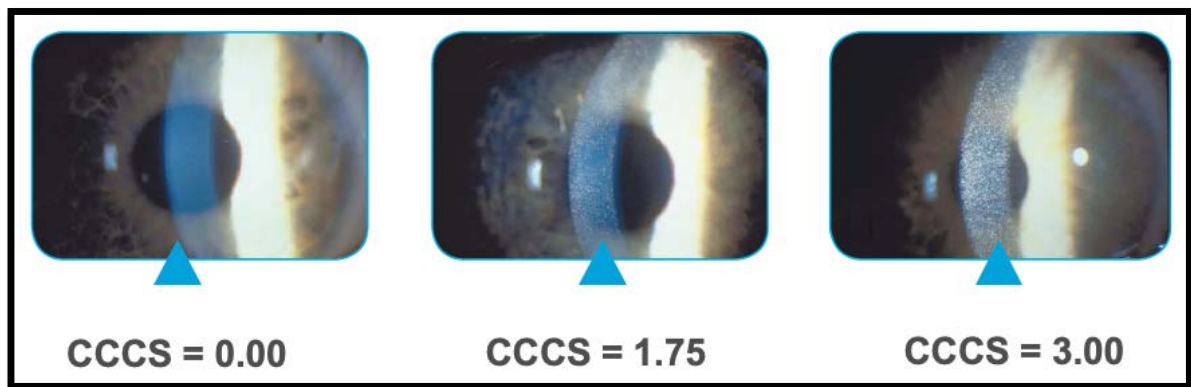


Figure 9: Slit-lamp library photographs showing examples of corneas with CCCSs of 0.00 to 3.00

2. Symptoms and evolution

The most frequent ocular complication in cystinosis patients is photophobia (light sensitivity) because of the light reflection caused by the crystals. Other symptoms are: eye pain, blepharospasm, keratopathies, reduced contrast visual acuity, punctate, and neovascularization of peripheral cornea. Cystine crystals ocular build-ups are mainly located in the conjunctiva and cornea, but also in the ciliary body, the iris, the choroid layer, the pigmented layer of retina and the capsule of lens. Cystine crystals develop first in the anterior corneal area during childhood and advances diffusely towards the posterior corneal area. Pigmentary retinopathy is also a known complication.⁷¹

See annex for a table of the evolution of ocular manifestations in cystinosis

3. Local treatment and management

Since the cornea is not vascularized, systemic cysteine-depleting therapy is useless in treating it. However, local cysteamine therapy is effective by disaggregating crystals and reducing photophobia.

Figure 9: Kowalczyk et al. "Diagnostics and treatment of ocular complications in infantile nephropathic cystinosis" *Ophthalmol J* 2021; Vol. 6, 206–214

⁷¹ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322

Hydrophilic cysteamine eye drops (solution):

Topical cysteamine eye drops as an aqueous solution were industrially developed by Sigma-Tau Pharmaceuticals and marketed in 2012 in the U.S.A. (Cystaran®). It consists in a 0.65% (6.5 mg per mL) Cysteamine Hydrochloride solution, corresponding to 0.44% (4.4 mg per mL) of active cysteamine. This formulation is not very convenient since it is required to be administered ideally every hour awake, or 6 to 12 times daily, and the bottle to be stored at very cold temperature because of oxidization (-20°C before opening, and refrigerated once opened).⁷² Thus, patient adherence to this treatment is an issue.⁷³ Among other limitations, we can also mention bad corneal penetration because of the corneal surface being lipophilic; thus, the quantity of cysteamine reaching the corneal stroma layer where crystals accumulate is not ideal.⁷⁴

Cystaran® has not been approved in Europe. Nevertheless, ophthalmic cysteamine solutions still exist as hospital and pharmacy off-license preparations in European countries, containing diverse compositions and CH concentrations (0.1%, 0.4%, 0.5%, etc).

Some adverse events were reported by patients treated with these eye drops (light sensitivity, eye pain, redness, irritation, visual alterations and headache) but they are considered more imputable to the disease rather than to the drops.

Viscous cysteamine eye drops (gel):

In response to the limitations previously mentioned of the existing ophthalmic cysteamine treatment, a novel formulation of cysteamine eye drops was developed by Orphan Europe (now RRD) in order to propose a topical treatment with a lower number of daily administrations.

The new formulation, named Cystadrops®, was approved in 2017 by the EMA, and got FDA approval in 2020.

⁷² Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322

⁷³ Biswas and Sornalingam. "The Ocular Status of Cystinosis Patients Receiving a Hospital Pharmacy-Made Preparation of Cysteamine Eye Drops: A Case Series." *Ophthalmology and therapy* vol. 8,1 (2019): 125-136.

⁷⁴ Makuloluwa and Shams. "CH eye drop solution for the treatment of corneal cystine crystal deposits in patients with cystinosis: an evidence-based review." *Clinical ophthalmology* vol. 12 227-236. Jan. 2018

It consists in a 0.55% (5.5 mg per mL) CH gel, corresponding to 3.8 mg per mL of active cysteamine. This formulation is meant to be administered 4 times daily in both eyes. The viscous agent in the product composition (carboxymethylcellulose sodium) helps cysteamine to be in contact with the eye during a longer period of time.

Regarding storage conditions, the bottle has to be kept refrigerated before opening, and can be left at room temperature during 7 days at most after.⁷⁵

A phase III clinical trial (comparative, open-label, randomized) was conducted by Dr. Liang in cystinosis patients of 2 years of age and above to compare efficacy between patients treated with 0.55% CH viscous drops (Cystadrops) and patients treated with 0.10% CH aqueous drops (standard French hospital preparation) during 90 days. Corneal cystine crystals build-up was significantly more reduced in patients treated with the gel-like drops from day 30 (assessed by IVCM).⁷⁶

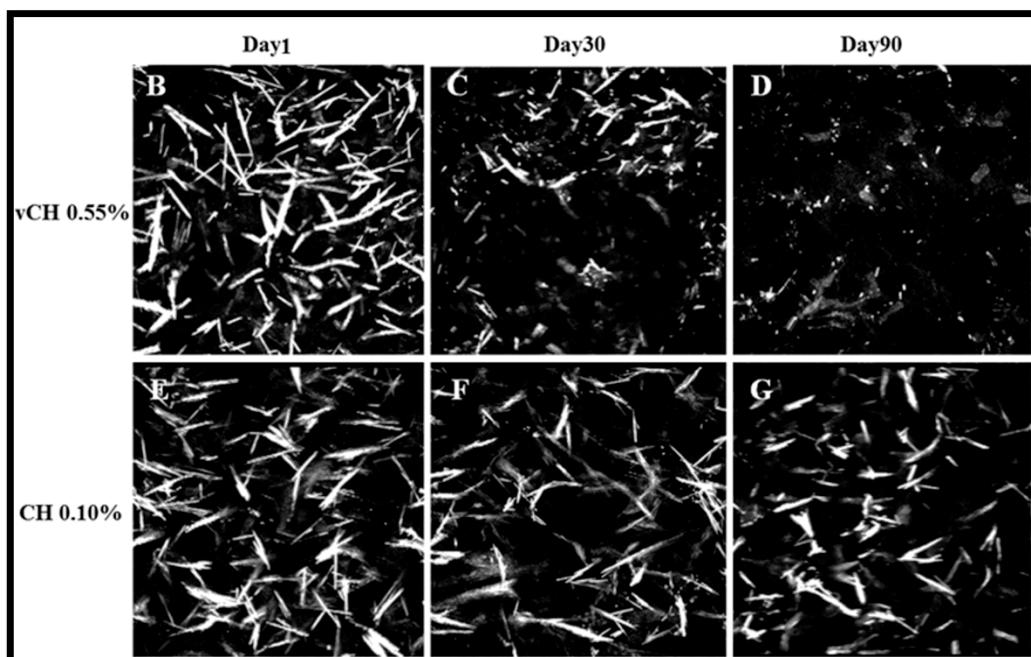


Figure 10: Changes Between Baseline and Day 90 with 0.55 CH viscous or 0.10 CH aqueous drops (assessed by IVCM)

The observed superior efficacy of the gel-like drops can be explained by a higher CH concentration and viscosity allowing longer time upon which cysteamine is in contact with the cornea and its inner layers.

⁷⁵ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322.

⁷⁶ Liang et al. "A New Viscous Cysteamine Eye Drops Treatment for Ophthalmic Cystinosis: An Open-Label Randomized Comparative Phase III" *Investigative ophthalmology & visual science* vol. 58,4 (2017): 2275-2283.

Less strict storage conditions and more convenient administration regimen of the gel formulation are meant to help the patient being adherent to the treatment.

Main reported adverse events for the viscous cysteamine solution are mild and consist in blurred vision, burning, eye pruritus, stinging, and eye irritation may be caused because of benzalkonium chloride (ophthalmic preservative). Soft contact lenses are incompatible with this treatment.

It would be interesting to have a future study evaluating differences between the 0.55% CH gel-like drops and the 0.44% CH hydrophilic solution regarding capacity to reduce corneal cystine crystals in the cornea of cystinosis patients.⁷⁷

See annex for summarized comparison of product information of Cystaran® and Cystadrops® from FDA prescribing information labels

Cornea transplantation:

In some very rare cases, untreated cystinosis patients suffer from severe corneal damage requiring cornea transplantation. Even after transplantation, cystine crystals can accumulate once again in the new cornea graft, so local cysteamine therapy should always be administered.⁷⁸

4. Monitoring

There are several ophthalmologic techniques in order to monitor cystine crystal accumulation and treatment efficacy in cystinosis patients' eyes.

Depending on the area targeted by the physician, either the cornea or the retina, methods used will be different.

Eye anterior segment: evaluating the cornea

Anterior Segment Optical Coherence Tomography (AS-OCT):

AS-OCT imaging is a non-invasive well tolerated technique using infrared radiation to obtain cross sections of the cornea in this case.

⁷⁷ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322.

⁷⁸ Emma et al. "NC: an international consensus document." *Nephrology, dialysis, transplantation - European Renal Association* vol. 29 Suppl 4,Suppl 4 (2014): iv87-94.

It is at the disposal of many ophthalmologists wanting to evaluate crystal accumulation in the cornea and especially how deep crystals diffused. Inconvenient is the high price of the OCT machine, and also the impossibility for infrared rays to penetrate the sclera and the iris.⁷⁹

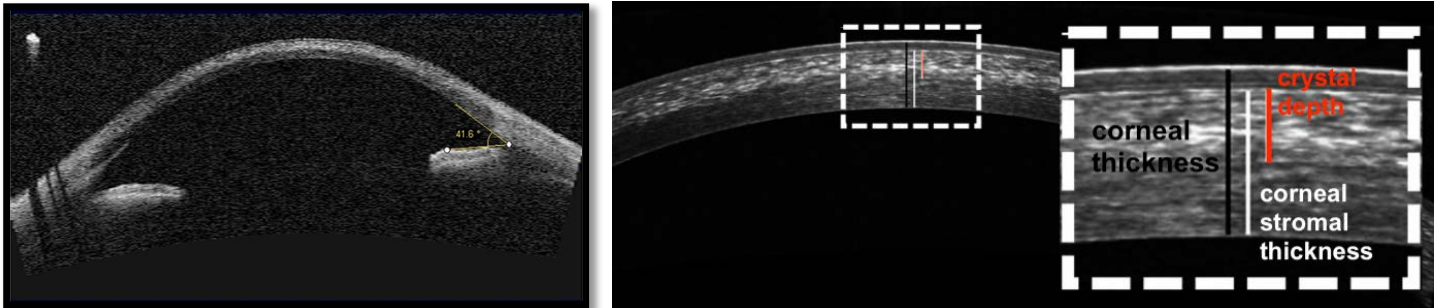


Figure 11: AS-OCT of the eye of a cystinosis patient

Ultrasound Biomicroscopy (UBM):

UBM uses ultrasounds for imaging the eye's anterior segment by non-invasive means. It allows the physician to visualize the evolution of the morphology and the topography of this area, but also the ciliary body and the iris, which was not the case with AS-OCT.

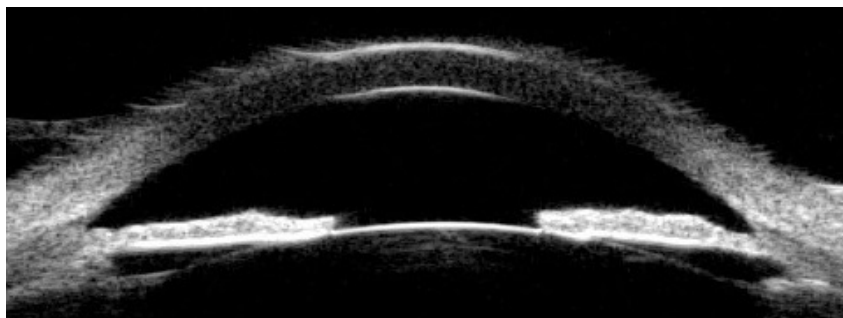


Figure 12: UBM imagery of the eye
(image from the American Academy of Ophthalmology)

In Vivo Confocal Microscopy (IVCM):

IVCM imagery produces high-definition and contrasted pictures of a plane area at a chosen depth. Corneal images obtained by IVCM in cystinosis patients are thereafter compared to standard images, allowing the physician to estimate the quantity of cystine crystals within the cornea with the help of a score (0 to 4).

⁷⁹ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322. Figure 11: left image from article above, right image from Keidel et al. "Establishing an objective biomarker for corneal cystinosis using a threshold-based Spectral domain optical coherence tomography imaging algorithm." *Acta ophthalmologica* vol. 99,2 (2021): e189-e195.

A total IVCM score is calculated by adding the individual scores of all cornea layers (0 to 28): both superficial and basal epitheliums, Bowman’s membrane, all three stroma areas (anterior, medium, posterior) and endothelium.

This technique informs the specialist not only about cystine crystal accumulation in the cornea but also inflammatory cells presence, damage in nerves, and efficacy of local cysteamine therapy. The machine used to perform IVCM is costly, so only specialized ophthalmology centers perform this test in 7 years old children and older.⁸⁰

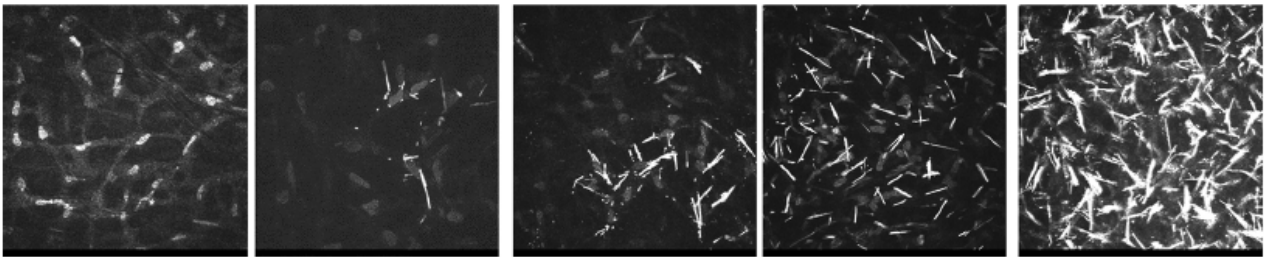


Figure 13: IVCM standardized images used to compare and grade pictures from cystinosis patients

Eye posterior segment: evaluating the retina

Widefield Retinal Imaging Using Optomap® (Optos):

Optomap® imagery provides ultra wide field images of the retina (200 degree view angle), displaying ~80% of the retina surface. This technique is well tolerated by all patients, including infants, because of the method relying on a laser source rather than usual light source, thus ignoring photophobia issues.

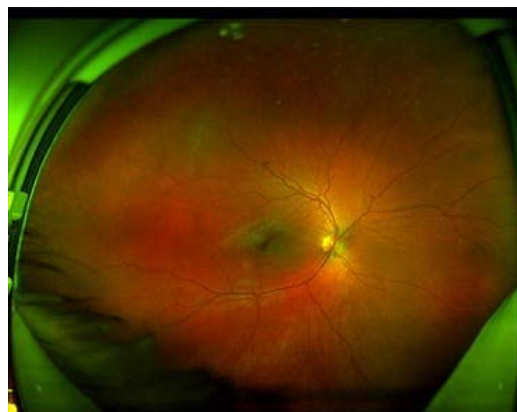


Figure 14: Optos® fundus photograph of a 15-year-old patient suffering from the infantile type of cystinosis

⁸⁰ Biswas et al. “Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum.” *Ophthalmology and therapy* vol. 7,2 (2018): 307-322.

Figure 13: from article above

Figure 14: from Pinxten et al. “Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis.” *Ophthalmology and therapy* vol. 6,1 (2017): 93-104.

Optical Coherence Tomography (OCT):

OCT can also be performed to obtain images of the retina and its layers, visualize crystal accumulation and measure retinal depth. This method also provides information regarding potential optic neuropathy and its evolution, and regarding intracranial hypertension. Even though OCT scanning renders high definition images of retina's anatomy, this technique unfortunately does not allow to quantify crystals formed in the retina.⁸¹

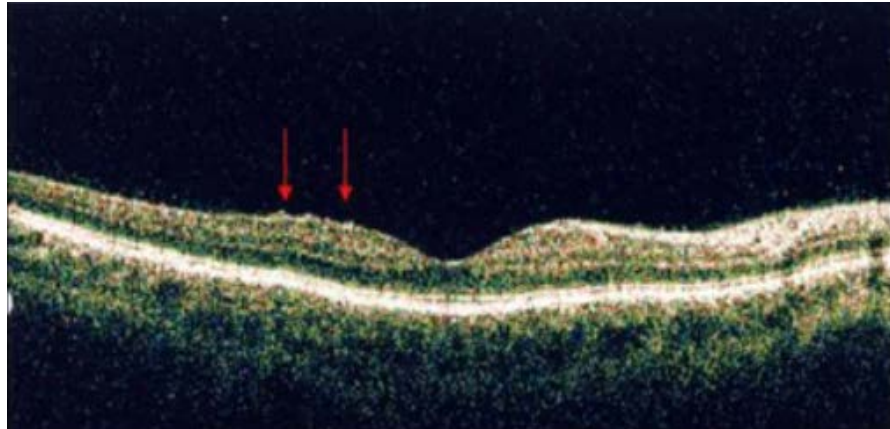


Figure 15: OCT image with red arrows indicating tiny deposits located in the superficial retina

See annex for a table listing advantages and disadvantages of all these methods

See annex for scheduling guidelines of ophthalmological monitoring visits in cystinosis patients

5. Issues and unmet needs

Patients and ophthalmologists still face several issues in the management of ocular cystinosis.

The first one is that eye drops, even viscous, still have to be instilled several times per day, on a life-long basis.

Marketed viscous cysteamine solution is only approved for patients above 2 years of age because the lack of clinical data on younger patients.

⁸¹ Biswas et al. "Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum." *Ophthalmology and therapy* vol. 7,2 (2018): 307-322. Figure 15: from Narendran et al. "Optical coherence tomography of macular crystalline opacities associated with chronic retinal detachment." *Eye* vol. 20,7 (2006): 843-5.

Patients report efficacy issues with cysteamine eye drops claiming the treatment does not work, and even more, worsens their QoL because of the topical pain and adverse events.

Actually, in most of these patients, it seems that eyes are fragile and damaged by other complications (for example inflammation), with an abraded corneal surface which is not suitable for cysteamine treatment right away. The ophthalmologist should first heal the eyes before focusing on dissolving cystine crystals in them.

Another issue encountered by patients on a more practical side is related to the treatment bottle and especially its drop squeezer. As of today, the squeezer is too hard for patients to pinch themselves because of their reduced muscle function. It is up to the pharmaceutical companies to work on these aspects too, on the manufacturing design of their products, to allow patients take their medicine.

6. How to improve patients' QoL

In order to improve cystinosis patients' QoL regarding their eyes, patients need to be referred quickly to a specialist ophthalmologist, with a continuous follow-up even after transitioning to adult care.

Recommendations and harmonized guidelines should be widely implemented in clinics managing cystinosis patients, with multi-disciplinary teams led by a key physician (for instance the pediatric nephrologist) coordinating the various investigations and appointments of the patients throughout this care continuum.

7. Research pipeline and ongoing studies

Research in ocular cystinosis is ongoing in both public and private sectors because of the need to develop more convenient and curative solutions to patients.

Cysteamine eye drops indication extension:

First, we can mention the “SCOB2”⁸² trial (Cystadrops in Pediatric Cystinosis Patients From Six Months to Less Than Two Years Old) conducted by RRD with Cystadrops in patients between 6 months and 2 years of age, in order to extend the product’s indication to this population of patients. The earlier patients are treated, the better for their eyes.

A sustained release cysteamine microsphere/thermoresponsive gel eyedrop⁸³:

Because of the several issues encountered with currently existing local cysteamine formulations, such as poor stability and the need of repeated daily administrations, researchers still aim to design better eyedrops.

A new reformulation of cysteamine was developed by a research team from the University of Pittsburgh (USA) consisting in a thermoresponsive gel containing polymer microspheres with cysteamine encapsulated inside.

Results from their latest preclinical (in vitro and in vivo) study are positive, showing improved stability of cysteamine up to 7 weeks (instead of 1 week for already marketed eyedrops) and cysteamine release over 24 hours with only one drop of gel equivalent to a daily course of administration of usual eyedrops. Future studies are planned in other animal models, and we can expect clinical application in the future.

Cysteamine-loaded contact lenses:

A novel approach is being developed in the form of cysteamine-loaded contact lenses. The goal is the same as for the gel formulation described above: reduce instillation frequency and avoid fast cysteamine degradation.

This approach has already been tested in a preclinical trial.^{84, 85}

⁸² <https://clinicaltrials.gov/ct2/show/NCT04125927>

⁸³ Jimenez et al. “A sustained release cysteamine microsphere/thermoresponsive gel eyedrop for corneal cystinosis improves drug stability.” *Drug delivery and translational research* vol. 11,5 (2021): 2224-2238.

⁸⁴ Biswas et al. “Latest Clinical Approaches in the Ocular Management of Cystinosis: Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum.” *Ophthalmology and therapy* vol. 7,2 (2018): 307-322.

⁸⁵ Dixon et al. “In vitro drug release and in vivo safety of vitamin E and cysteamine loaded contact lenses.” *International journal of pharmaceutics* vol. 544,2 (2018): 380-391.

It was demonstrated that cysteamine diffuses out rapidly from all lenses tested, that vitamin E addition improves release duration, and an estimated treatment regimen consists in wearing the lenses around 5 hours each day, which is representative of normal contact lenses usage.

This treatment option would allow patients to receive cysteamine during several hours progressively delivered to their cornea, while also benefiting from a potential sight correction if necessary.

Gold nanoparticles-loaded contact lenses:

Another recent in vitro research project involving contact lenses exists, it is called "GoldinLens". This lens is manufactured with the incorporation of gold nanoparticles inside. In this case, there is no pharmacological effect expected: the gold particles trapped inside the lens directly bind to the cystine present at the surface of the cornea due to the affinity between cystine and gold.⁸⁶

While the advantage of a drugless solution includes not involving conservative and potentially irritative agents, questions remain regarding efficacy and ability to reduce cystine crystals in the medium and deeper layers of the cornea because of relatively low permeability of the cornea, but also regarding the altered transparency of the lens due to gold particles not being small and sparse enough.

While the manufacturing process to develop this lens is quite effective, it is hard to tell if further research will be performed allowing use of GoldinLens in cystinosis patients one day.

Biomaterial mediated transfer of CTNS gene⁸⁷:

The development of a localized gene delivery system for the treatment of cystinosis aims to reduce safety concerns usually inherent to systemic gene therapy and to target organs that are unreachable through a systemic pathway, such as the eye cornea.

⁸⁶ Liu et al. "Gold nanoparticle synthesis in contact lenses for drug-less ocular cystinosis treatment." *European journal of pharmaceuticals and biopharmaceutics e.V* vol. 165 (2021): 271-278.

⁸⁷ Graceffa "Development of a fibrin-mediated gene delivery system for the treatment of cystinosis via design of experiment." *Scientific reports* vol. 12,1 3752. 8 Mar. 2022

This is the purpose of the recent research work of Dr. Graceffa from Ireland: designing a fibrin-mediated gene delivery system for the treatment of ocular cystinosis. This in-vitro study was performed with fibrin hydrogels releasing non-viral plasmids encoding for CTNS on fibroblasts from a cystinosis patient. Different components concentrations of the delivery system were evaluated using an engineering methodology to obtain an optimized delivery system allowing the best gene transfection possible.

Fibroblasts studied, after being in contact with the biomaterial carrying the CTNS genes, effectively expressed recombinant CTNS and showed decreased cystine levels.

This potential therapeutic solution is still far from ready to be used in humans, yet the innovative approach and promising results so far provide new insights from the treatment of ocular cystinosis and the local use of gene therapy.

Innovative single cysteamine eye drops doses:

In late 2022, a research team published an article about the development of cysteamine eyedrops in hyaluronic acid packaged in innovative single-dose systems in a hospital pharmacy department⁸⁸.

The idea of having unitary doses of cysteamine eye drops is not new, but previous industrial projects to develop and ultimately market such formulation did not succeed.

The advantage of having single dose packaging for cysteamine eyedrops lies in preventing a large amount of eyedrops solution from being decomposed. Only the daily amount used would be in contact with air, leaving the rest of single doses sealed and stocked somewhere at low temperature. Not only drug stability would be allowed with this formulation but also handling and transportation by patients.

Ideally, patients should have the choice in the future between bottle or single doses packaging, which is the case for many ophthalmological eyedrops in other diseases.

⁸⁸ Castro-Balado et al. "Cysteamine Eye Drops in Hyaluronic Acid Packaged in Innovative Single-Dose Systems: Stability and Ocular Biopermanence." *Pharmaceutics* vol. 14,10 2194. 15 Oct. 2022

VI. Cystinosis patient journey

Considering a rare disease such as cystinosis, describing as accurately as possible the typical cystinosis patient journey will help healthcare professionals to understand the patient's disease management, from diagnosis to adulthood and further.

See annex for the figure describing cystinosis patient's journey from ERKNet

VII. Guidelines & standard of care

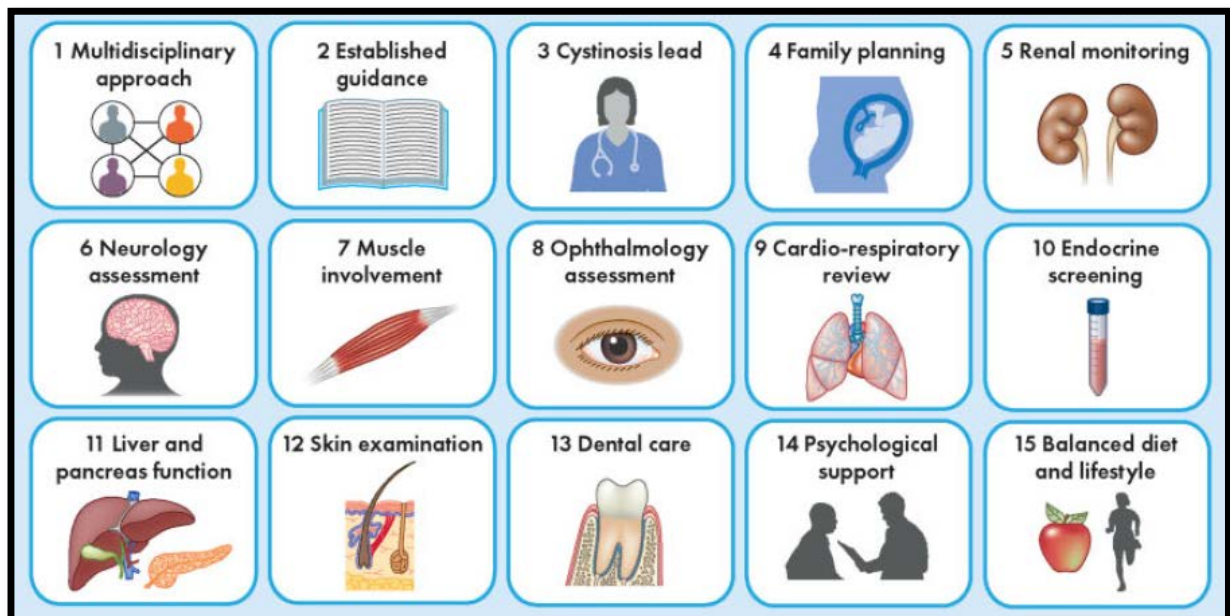


Figure 16: 15 recommendations on cystinosis management and the creation of a cystinosis consultation checklist

In the 2022 Clinical Kidney Journal, Dr. Levtchenko et al. published new international expert guidelines for the management of both adolescent and adult cystinosis patients by multidisciplinary teams.⁸⁹

⁸⁹ Levtchenko et al. "Expert guidance on the multidisciplinary management of cystinosis in adolescent and adult patients." Clinical kidney journal vol. 15,9 1675-1684. 15 Apr. 2022

All 15 recommendations are detailed in the article and were built by these international experts from already existing guidelines, clinical practice and strategies.

The aim of these standardized instructions is to help healthcare professionals to act precisely and quick when facing a patient with cystinosis for the patient to have the best overall prognosis possible, in all therapeutic areas where cystinosis leads to complications.

VIII. How to stay tuned

1. Events and congresses

For patients, healthcare professionals, and pharmaceutical companies, staying up to date regarding the latest research works, protocols, trials, therapeutic solutions is essential.

There are many congresses, focused on rare diseases, pediatric nephrology, ophthalmology, etc., among which there are regularly conferences and symposia about cystinosis advancements.

We can mention for example

- the International Cystinosis Conference, organized by the Cystinosis Network Europe (CNE) once every two years, maybe the most important event for cystinosis
- European Society of Pediatric Nephrology (ESPN) annual congress
- American Academy of Ophthalmology (AAO) annual congress
- European Pediatric Ophthalmological Society (EPOS) annual meeting
- Cystinosis Academy, virtual event organized by RRD

For instance, during 2020's International Cystinosis Conference held virtually, 49 countries were involved with conferences translated in 8 languages, with an attendance of over 950 viewers.

During these events, experts and non-expert physicians and other healthcare practitioners from all around the world gather to share clinical practice, cases, insights and new data published or not.

These events rely on the scientific societies but also on the sponsorship of private companies, and on the important involvement patients associations.

2. Cystinosis community

The cystinosis community not only includes patients, physicians, researchers and pharma companies but also networks and associations participating from the very beginning of cystinosis awareness in gathering information and people together. These associations, mostly composed of family volunteers, do a tremendous work to raise awareness about the disease, its unsolved problems, and many patients' complaints as queries towards HCPs and industrial companies, each party having its own focuses and interests.

Combining the needs and thinking about solutions involving all members of this community is the good way to proceed towards patient's benefit and alleviation of the disease burden.

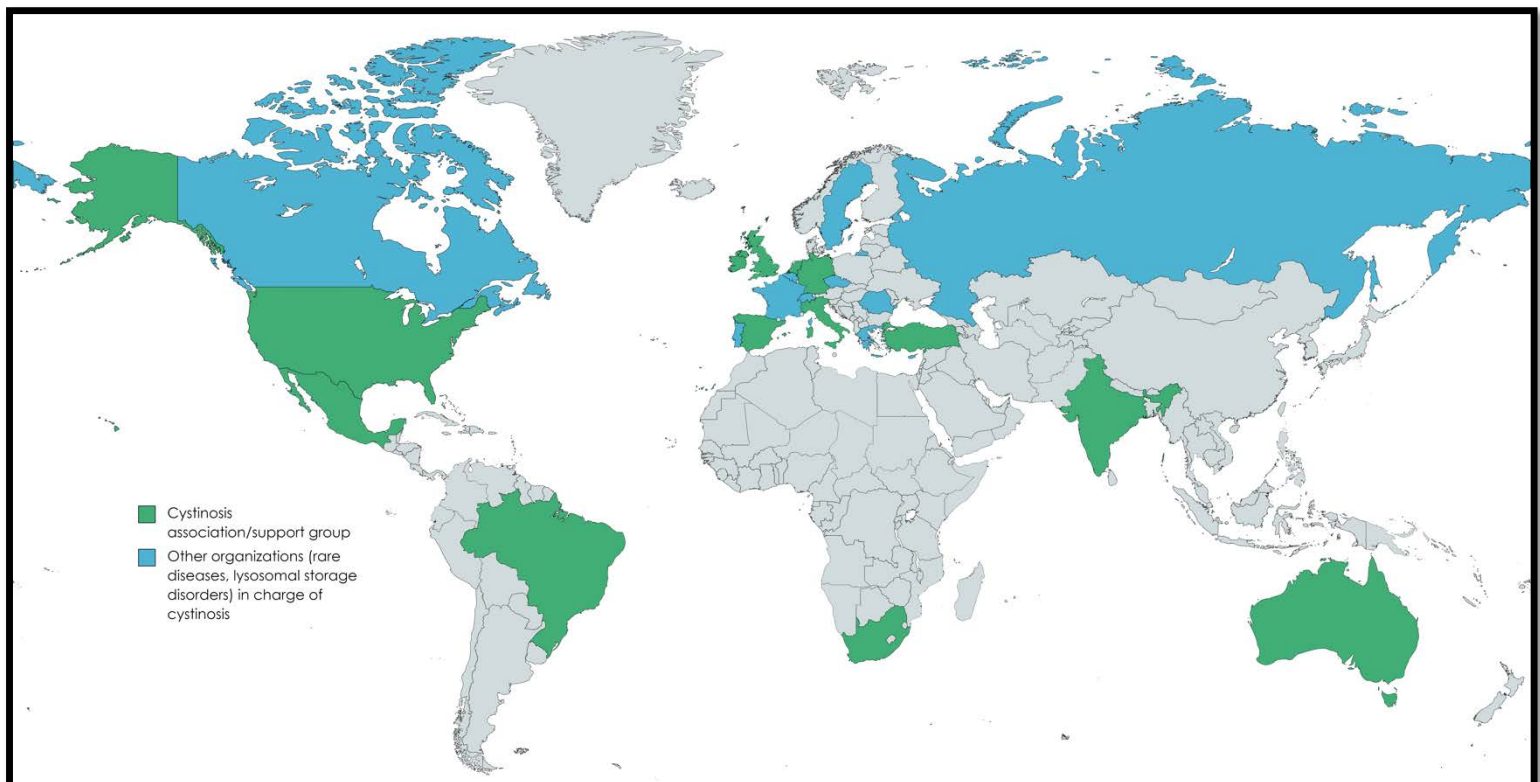


Figure 17: World map of cystinosis associations or related associations in charge of cystinosis

IX. Discussion, future and unsolved questions

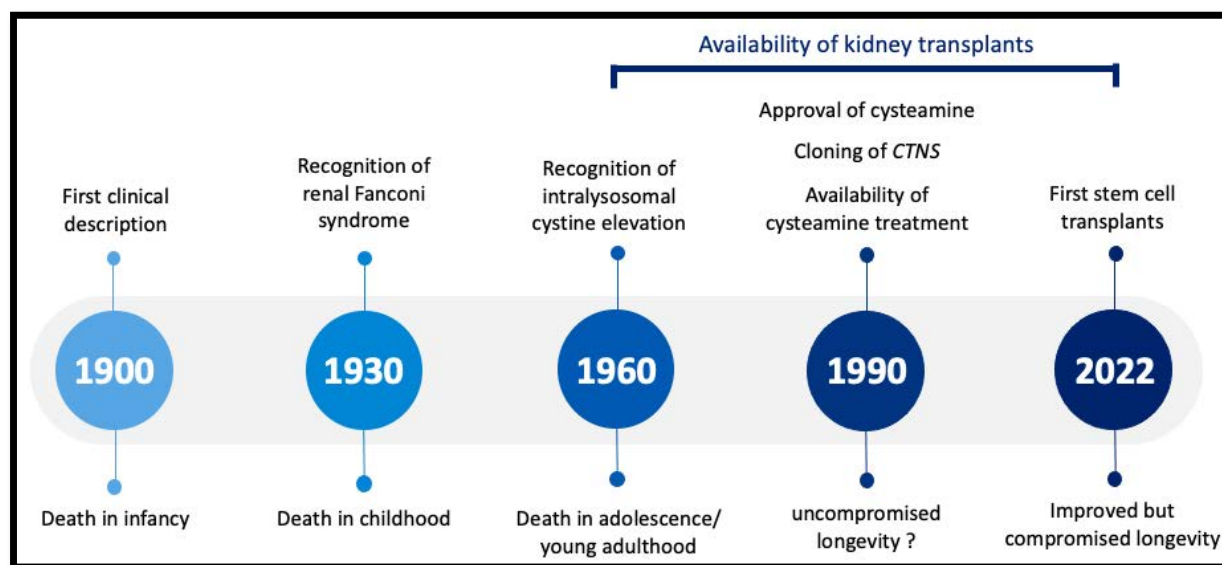


Figure 18: Cystinosis timeline

Thanks to cysteine-depleting therapy through cysteamine treatment, either systemic or local, cystinosis patients' prognosis was revolutionized.

This being said, cysteamine is still not the panacea since it does not cure the patients and does not correct the lysosomal transport of cystine. Different forms and dosages of cysteamine have been developed to improve treatment adherence, convenience and efficacy. Some physicians even combine immediate release and delayed release cysteamine intake to optimize treatment regimen. But at the end of the day, cysteamine therapy only delays renal and extra-renal complications. Moreover, it does not affect at all other impaired pathways and mechanisms linked to the lysosome that lead to known and unknown issues.

Investigating and identifying these interactions and new targets will surely help in the development of innovative and promising therapies. To that extent, diverse cellular and animal models were designed for a better understanding of the disease. Also, with current machines and technology advancing over and over, diagnosis sensitivity will constantly improve, allowing for example a future implementation of newborn screening programs as well established and accepted preventive solutions. Ongoing research is also focused on the testing of better and more specific biomarkers, for a precise, convenient and accessible monitoring of disease progression and treatment efficacy in patients.

Research pipeline in cystinosis is currently full of very innovative solutions, among which some of them being curative. Gene therapies with a functional

CTNS gene transfer would allow patients to have a fully restored cystinosis function and an improved quality of life. But even if such solutions will be evaluated as successful and be marketed someday, it is unlikely that a majority of patients will benefit from them because of costs and accessibility.

Effective treatments will be useless if patients are not diagnosed and treated early enough, hence the absolute need of generalizing newborn screening.

Undesired effects and non-adherence are also preoccupying issues to be addressed in the current standard of care.

Focusing on treating earlier, treating other causes and complications besides cystine-depletion and having a more holistic view of patient's journey is the challenge the cystinosis community is currently facing. Encouraging preclinical results in some novel treatment approaches, such as hematopoietic stem cell transplantation, gives hope and it might be the beginning of a new era in treating cystinosis, this time for good, but only time will tell.

X. Conclusion

Cystinosis is a very interesting disease, and turns out to be a “good model” of rare metabolic disease from which to draw many lessons and applications in other similar diseases. Prognosis in cystinosis patients and disease awareness are constantly going forward, thanks to an amazing community eager to share findings, recommendations, advices, activities and partner altogether, seeking the best solutions one could imagine for the benefit of the patients.

This thesis is meant to allow extensive comprehension of the disease, of current and future treatments and unmet needs to students, scientists, physicians, patients and peers by assembling and organizing scientific information from what is published but also from my experience as a medical affairs employee in a pharmaceutical company taking into consideration expertise and feedbacks from senior employees, expert clinicians and patients associations.

There are still many areas for improvement.

Some key unmet needs to remember are as following:

- Approved treatments in cystinosis as of early 2023 are focused on the symptoms of the disease, and are life-long therapies
- Inconsistent adherence to the treatment is a big issue in cystinosis
- Early diagnosis is insufficient while it is key for good prognosis
- Transitioning from child care to adult care is a big challenge for patients but also families and physicians

Some solutions to the issues listed above:

- Continue collaboration for developing and ultimately market efficient and safe curative therapies such as gene therapy and tolerance induction
- Find innovative solutions with lightened dosage regimens, practical packaging, less debilitating side effects or resolving those to improve adherence
- Implementing newborn screening taking into consideration local population specificities regarding CTNS mutations and genotype
- Offering trainings and tools to healthcare practitioners, patients and families, for them to understand better the disease and its challenges, to have an appropriate approach depending on disease severity, patient psychological profile and age

From a pharmaceutical company's point of view, issues regarding access to existing treatments are still to be addressed, especially in developing countries: in Latin America, Asia and Africa. Supply problems sometimes occur and may lead to patients left untreated. Collaboration between companies, physicians, patients, associations and national agencies will hopefully increase through more expanded access procedures, clinical trials, real world evidence studies, patient registries; allowing patients to benefit from the latest diagnosis and therapeutic approaches available, allowing physicians to treat their patients, and allowing companies to grow and gather valuable health data.

Such collaboration should also happen at earlier stages of development, and daily practical aspects from patients' lives taken into account when designing a treatment and a trial. When pharmaceutical companies only focus on efficacy, safety and the scientific aspect of their product, unanticipated practical problems may prevent patients from taking their treatment whether directly or indirectly.

From a national health authority perspective, it should not be forgotten that rare diseases are a special area where different rules apply, economically and scientifically wise. In my opinion, the greatness of a society or civilization depends on its capacity to take care of the weak and isolated. While pharmacoeconomic aspects are also key to make future diagnosis and treatment options available such as generalized newborn screening and gene therapy, we should not forget that it is not only about the healthcare costs such solutions would alleviate or reduce. And more importantly, in the case of cystinosis, having approved life-long symptomatic treatments is encouraging and saving patients but it is not enough. Fortunately, cystinosis patients now survive, but the cystinosis community fights and aims for patients to be diagnosed at the earliest stage possible, to be cured from their disease and hopefully someday live a normal and fulfilling life.

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Annex

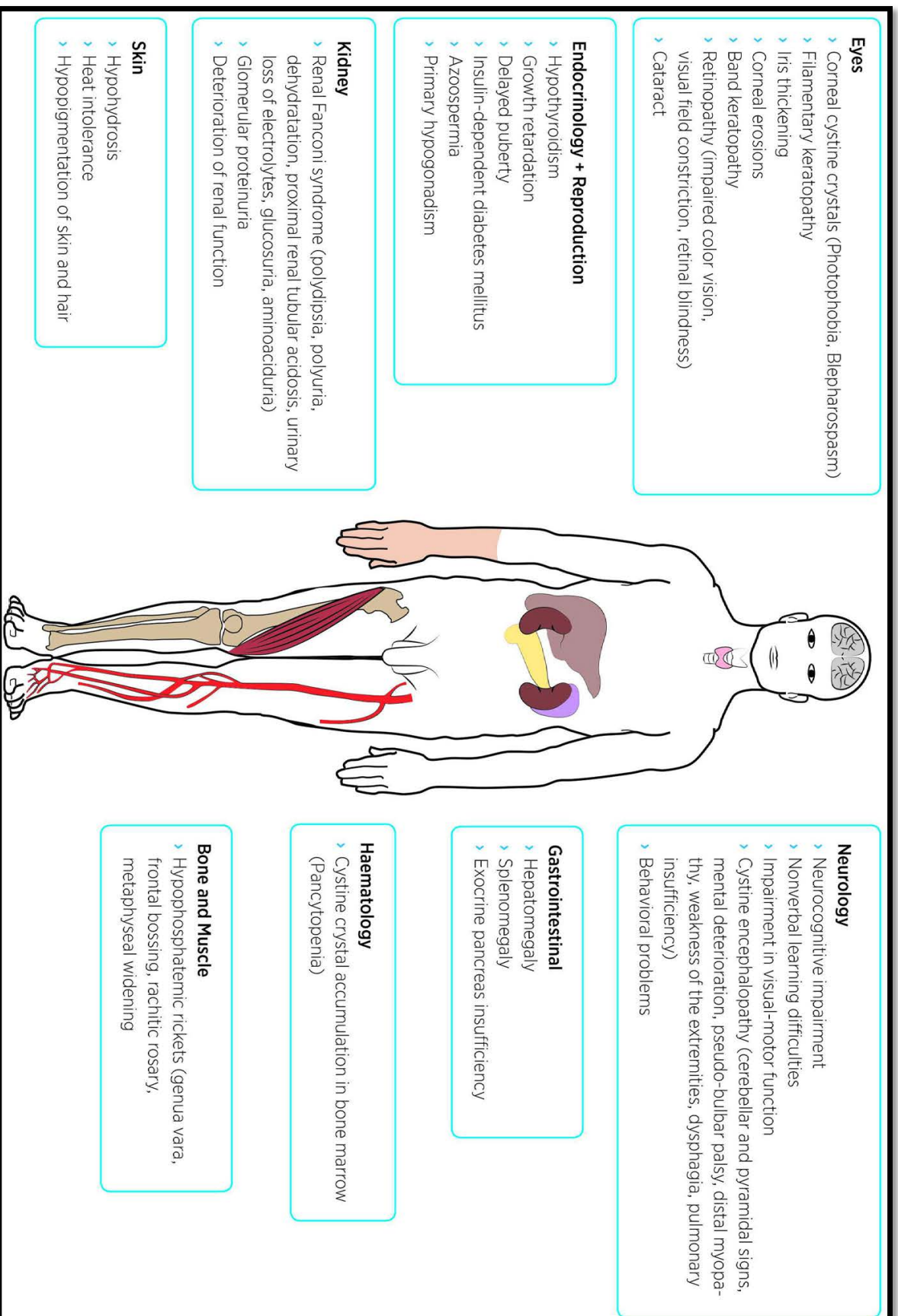


Figure 19: Possible symptoms and disease manifestations of nephropathic cystinosis.

	< 1 year	1-2 years	3-4 years	7-10 years	Puberty	2 nd & 3 rd decade of life
Age-dependent general signs and symptoms	Failure to thrive, rickets, growth disorders, light hair and blue eyes in Caucasian patients ⁽²⁾			Severe symptoms, thyroid insufficiency (50%) ⁽³⁾	Delayed sexual maturation, Hypogonadism ⁽⁴⁾	Symptomatic CNS involvement (2%), CNS calcification (15%), myopathy (20%), diabetes mellitus, liver disease, male hypogonadism (70%), pulmonary dysfunction (100%) ^(4,5)
	Fanconi syndrome at 6 to 12 months (95%) ⁽³⁾	Polyuria, polydipsia ⁽¹⁾ , progressive reduction of the glomerular filtration rate, Fanconi syndrome ⁽⁴⁾	Progressive renal failure; final stage of renal insufficiency in the first decade of life (ESRD) ⁽¹⁾	Progressive renal failure; final stage of renal insufficiency in the first decade of life ⁽⁶⁾	Terminal renal failure (prevalence chronic renal failure 95%), kidney transplant ⁽³⁾	
Age-dependent nephrological signs and symptoms						

Table 3: Age-dependent general and renal signs in cystinosis patients

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Table 4: Overview of treatments in NC patients

	Drug	Daily dose	Frequency	Remarks
A. Cystine-depleting therapy				
Systemic administration	Immediate-release cysteamine bitartrate	<12 years: 1.3–1.95 g/m ² /day	QID	Start at a low dose (one-sixth of the target dose) and increase gradually over 6–8 weeks
	(Cystagon - Mylan Pharmaceuticals, UK)	>12 years: 2 g/day		Do not exceed max dose of 1.95 g/m ² /day
	Extended-release cysteamine bitartrate (Procysbi - Raptor Pharmaceuticals, Novato, CA, USA)	Start with 80% dose of the Immediate-release formulation	BID	Regular assessment of the leucocyte cystine level (LCL) is recommended (children three to four times per year, adults: one to two times per year). Aim for LCL < 0.6 nmol cystine/mg protein
				In case of side effects: Gastrointestinal complains: add proton pump inhibitor Skin striae, angioendotheliomatosis: perform dose reduction with 25–50%
Corneal cystinosis	Cysteamine hydrochloride 0.44–0.55% ocular topical solution (eye drops)		6–12 times daily	Yearly ophthalmological follow-up is recommended. with slit-lamp examination, OCT
Topical treatment	(Cystaran O, 44% Sigma-Tau Pharmaceuticals, Gaithersburg, MD, USA)			Careful for eye burning symptoms in case of corneal erosions
	Cysteamine ocular gel (eye gel) (Cystadrops - Recordati, Milan, Italy)		QID	
B. Supportive treatment - B.1 Substitution of losses				
<i>Renal Fanconi syndrome</i>				
Polyuria	Free access to water and toilet			Avoid prolonged exposure to sun and heat; special attention to hydration in case of diarrhea, vomiting
Renal salt losing	Sodium potassium citrate	2–10 mmol K/kg/day	QID	Administer in between meals
	Sodium bicarbonate	2–15 mmol /kg/day	QID	
Potassium losses	Potassium citrate	2–10 mmol K/kg/day	QID	Aim for a potassium level >3 mmol/l.
	Potassium phosphate	0.6–2 mmol phosphate/kg/day	QID	Trough levels should be monitored before administration of the next dose
Alkali losses	Citrate or bicarbonate as sodium and potassium salts	5–15 mmol/kg/day	QID	Aim for a normal bicarbonate level (21–24 mmol/l)
Phosphate losses	Phosphate in potassium or sodium salts	30–60 mg elementary phosphate/day	QID	Aim for age-related normal phosphate levels
				High doses of phosphate supplements can cause or aggravate nephrocalcinosis Trough levels should be monitored before administration of the next dose
Difficult to control electrolyte losses and polyuria	Indomethacin	0.5–3 mg/kg/day	TID	Monitor renal function Discontinue in case of dehydration Concomitant use of ACE-inhibition is contra-indicated

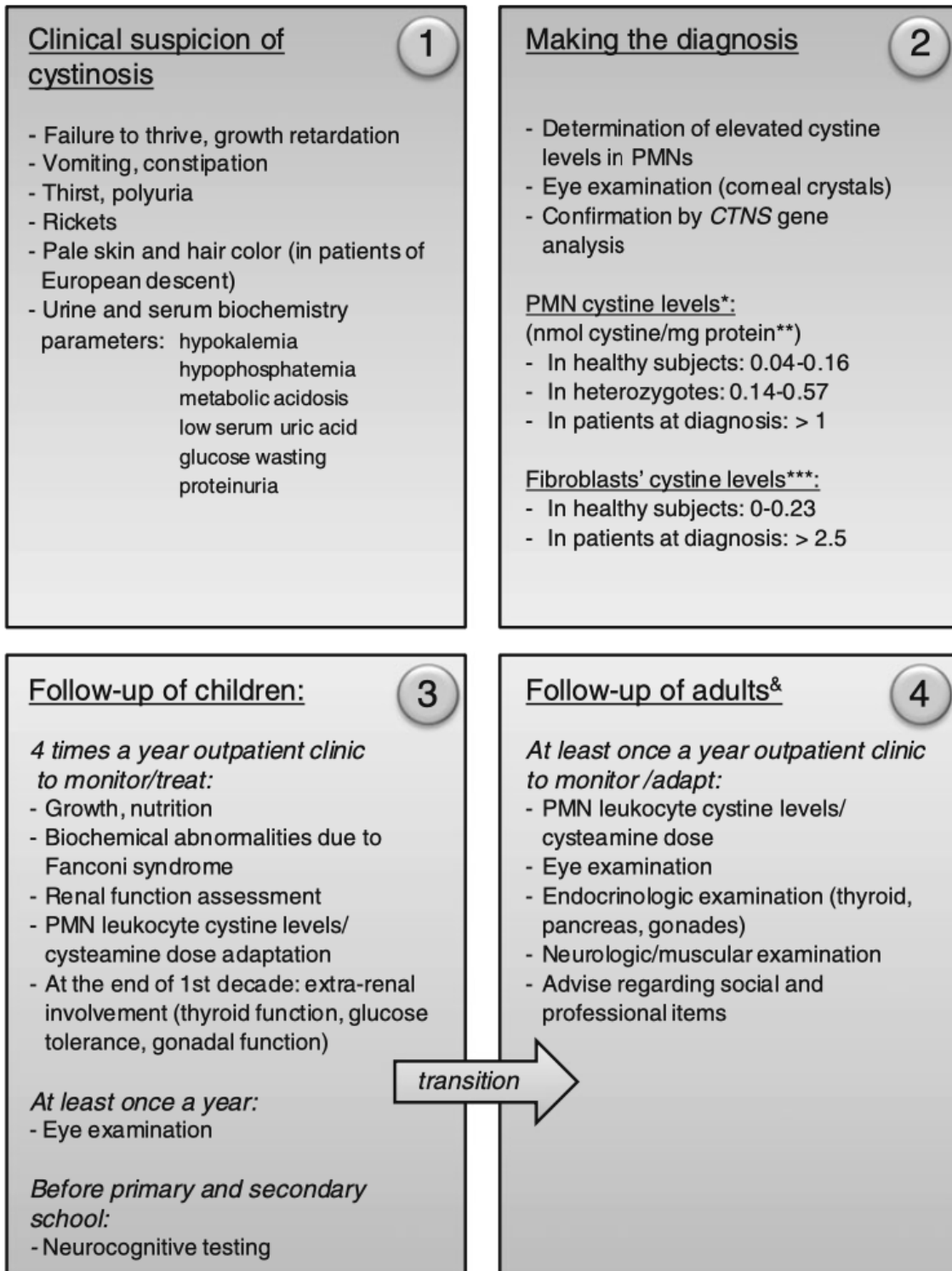
Veys et al. "Nephropathic cystinosis: an update." Current opinion in pediatrics vol. 29,2 (2017): 168-178.

Table 4 (continued): Overview of treatments in NC patients

	Drug	Daily dose	Frequency	Remarks
Proteinuria	ACE-inhibition: enalapril	0.10–0.25 mg/kg/day	QD	Monitor renal function and serum potassium Preferable administration at night to avoid hypotension Concomittant use of Indomethacin is contraindicated
Rickets	1-Alpha-hydroxycholecalciferol	0.5–2 µg/day	Single dose	Beware of hypercalcemia; monitor serum calcium concentration
Carnitine losses	L-carnitine	20–30 mg/kg/day	TID	
Copper deficiency	Copper supplementation			1–10 mg/day depending on age and serum copper levels Chlorophyllin tablets that are used to mitigate halitosis contain 4 mg of elemental copper per tablet
B.2 Nutritional support				
Malnutrition	High caloric intake	130% of RDI		Consider tube feeding in young infants
B.3 Hormonal replacement				
Growth retardation	rhGH			Only to be considered for early initiation in case of optimal feeding schedule, adequate control of electrolyte balance and treatment of rickets, and normal eGFR Higher doses of phosphate may be needed
Hypothyroidism	Levothyroxin	<12 years: 5 µg/kg >12 years: 2–3 µg/kg Adults: 1.7 µg/kg	QD	Start at 25% of the daily recommended dose, and increase gradually to a full dose in 4 weeks
Glucose intolerance	Insulin	According to insulin need		Blood glucose monitoring; Regular assessment of HbA1c

Veys et al. “Nephropathic cystinosis: an update.” Current opinion in pediatrics vol. 29,2 (2017): 168-178.

Figure 20: overview of the recommended follow-up in NC patients



* Values provided by Laboratory of Genetic Endocrine and Metabolic Diseases, Radboud University Nijmegen Medical Centre, The Netherlands (Dr. L. Kluijtmans)

** In the literature cystine is frequently expressed as ½ cystine/mg protein.
 ½ cystine/mg protein = 2 x cystine/mg protein

*** Cystine measurements in cultured fibroblasts can be used for the confirmation of the diagnosis, when molecular analysis of the *CTNS* gene is not available.

[&] Most adult patients are transplanted and are followed by adult nephrologists; the scheme of nephrologic follow-up is not included in this figure.

< 1 year	No signs before the age of 1 ⁽¹⁾ , initially asymptomatic ⁽³⁾	1 - 2 years	Corneal crystals visible after 16 months ⁽¹⁾ , no symptoms yet ⁽³⁾	3 - 4 years	Accumulation of corneal crystals, crystal deposits in the anterior and increasingly in the posterior periphery; pigmentary mottling ⁽¹⁾ ; early photophobia ⁽³⁾	7 - 10 years	Crystals in the entire periphery of the stroma and in the endothelium ⁽¹⁾ ; progressive photophobia (prevalence 50%), blepharospasm ⁽³⁾	Puberty	Superficial punctate keratopathy, macula anomalies ⁽¹⁾ ; the feeling of a foreign body in the eye and pain ⁽³⁾	2 nd & 3 rd decade of life	Filamentous and band keratopathy, neovascularisation of the corneal periphery, crystals in the entire corneal stroma structures ⁽¹⁾ ; decreased visual acuity, reduced colour vision and reduced peripheral vision and night vision, retinal blindness ⁽³⁾ , corneal transplant ⁽¹⁾
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Table 5: evolution of ocular manifestations in cystinosis

	Aqueous drops / Cystaran®	Viscous drops / Cystadrops®
Indication	Treatment of corneal cystine crystal accumulation in patients with cystinosis.	
Dosage (active cysteamine)	4.4 mg/mL	3.8 mg/mL
Administration	one drop in each eye, every waking hour	one drop in each eye 4 times a day during waking hours
Adverse reactions	<ul style="list-style-type: none"> - sensitivity to light - redness - eye pain/irritation - headache - visual field defects 	<ul style="list-style-type: none"> - pain - blurred vision - eye irritation - ocular hyperemia - instillation site discomfort - eye pruritus - increased lacrimation - ocular deposits.
Storage conditions	<ul style="list-style-type: none"> - Store in freezer at -25°C to -15°C. - Thaw for approximately 24 hours before use. - Store thawed bottle at 2°C to 25°C for up to 1 week. Do not refreeze. - Discard after 1 week of use. 	<ul style="list-style-type: none"> - Store in the refrigerator (2°C to 8°C). - Store opened at room temperature (20°C to 25°C). - Keep the bottle tightly closed in the outer carton in order to protect from light. - Discard 7 days after first opening.

Table 6: Product information of Cystaran® and Cystadrops® from FDA prescribing information labels

Technique	Advantages	Disadvantages
AS-OCT	<ul style="list-style-type: none"> - Well tolerated, as it uses an infrared light source (no photophobia issue) - Non-invasive - Rapid image acquisition (0.25 s) - Semi-automated image analysis 	<ul style="list-style-type: none"> - Machine is expensive - Tissue penetration can be limited, as it is unable to visualize through the iris and sclera - Unable to accurately quantify the amount of deposits within the cornea
UBM	<ul style="list-style-type: none"> - Provides high-resolution visualization of iris position - Enables visualization of morphological and topographical changes in the anterior chamber angle 	<ul style="list-style-type: none"> - May cause discomfort, as it uses a probe that requires an immersion technique (a saline-filled eye cap can, however, be adapted to the probe) - May cause abrasion and infection, and anterior segment deformation - Patients must be in a more supine position and may require general or local anesthetics - Time-consuming - Requires a trained operator
IVCM	<ul style="list-style-type: none"> - High-resolution - Tissue components can be easily visualized, e.g. nerves, cells, blood vessels and connective tissue - Gives a precise localization of the depth of corneal crystal deposition - Only way to analyze crystal deposits at a cellular level in the cornea, limbus and conjunctiva - Most useful for quantitative analysis of therapeutic interventions for corneal disease - Able to simultaneously assess corneal comorbidities 	<ul style="list-style-type: none"> - Machine is expensive - Requires an experienced ophthalmologist or well-trained technician to acquire good quality images
Optomap®	<ul style="list-style-type: none"> - Enables a large area of the retina to be captured - Can be magnified to a high depth - Well tolerated as it uses scanning laser rather than regular light - Can be used to obtain an autofluorescence capture of the fundus to measure RPE function and damage 	<ul style="list-style-type: none"> - Imaging of the far superior and inferior peripheral retina is less complete compared with that of the temporal and nasal retina - Obvious distortion and decreased resolution of the far temporal and nasal peripheral retina
OCT	<ul style="list-style-type: none"> - Rapid image acquisition of the structural view of the retina - OCT scans (10,000 images/s) enable highly detailed anatomical analysis of the retinal layers 	<ul style="list-style-type: none"> - Limited tissue penetration (unable to visualize through the iris and sclera) - Unable to accurately quantify the amount of crystal deposits within the cornea

Table 7: Advantages and disadvantages of diagnostic techniques for imaging anterior and posterior segments of the eye

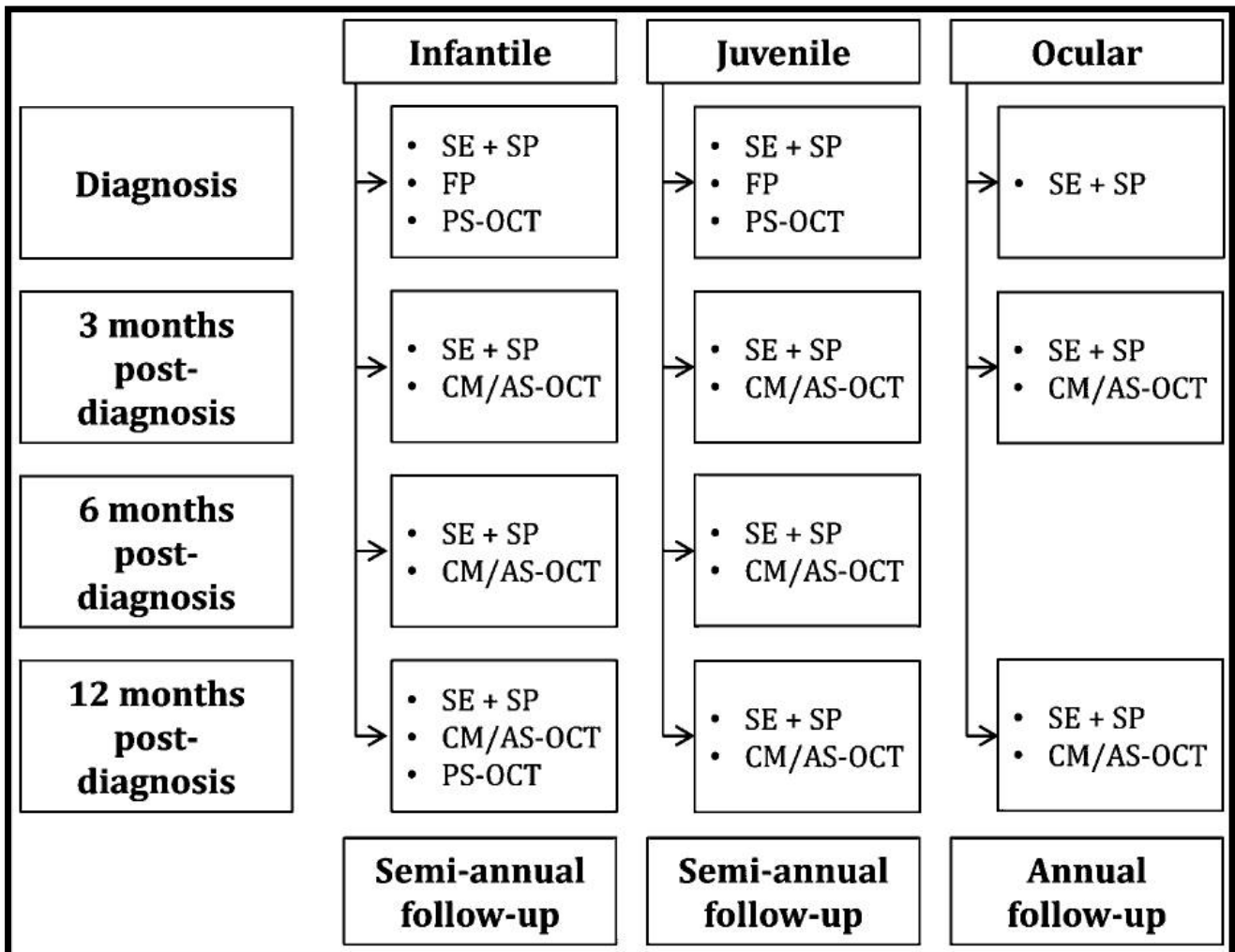


Figure 21: The standardized clinical ophthalmological assessment, a protocol for follow-up of patients with cystinosis.

AS-OCT anterior segment optical coherence tomography, CM confocal microscopy, FE fundus examination, FP fundus photography, SE standard examination, PS-OCT posterior segment optical coherence tomography, SP split-lamp photography. Standard examination (SE) includes history, visual acuity, tonometry and slit-lamp examination

Pinxten et al. "Clinical Practice: A Proposed Standardized Ophthalmological Assessment for Patients with Cystinosis." Ophthalmology and therapy vol. 6,1 (2017): 93-104.

Cystinosis Patient Journey

ERKNet

European Reference Network
for rare or low prevalence complex disorders

Note: Cystinosis is complex, no clinician can know all symptoms

Note: A well treated child with cystinosis can live a normal life



<p>1. First Symptoms Glucosuria, but no diabetes. Not all symptoms start at the same time. Renal Fanconi syndrome causing: Polyuria, vomiting, constipation or diarrhoe, general malaise and fatigue, excessive thirst, growth retardation, rickets. Photophobia; nutritional problems; "weak" bones; some children stop walking, toilet trained children lose this ability again (because of the amount of fluid).</p>	<p>2. Diagnosis Cystine measurement out of white blood cells to be done in a trained laboratory. Genetic testing. Newborn screening.</p>	<p>3. More symptoms Learning disabilities caused by: chronic fatigue, visual-spatial problems, some fine motor skills limitations. BUT: Normal intelligence, other cognitive functions are usually preserved. Delayed puberty, infertility in men. And many more ...</p>	<p>4. Treatment & Surgery At the moment there is only one medication (Cysteamine) to slow down progression of cystinosis. Dialysis and kidney transplantation can be avoided for a long time. Patient can fall dehydrated and creatinine rises very fast again when fluids are restricted after transplantation.</p>	<p>5. Adulthood Pregnancy: women can have children, they are not affected by cystinosis. Cystinosis can show many severe symptoms in patients not well treated from the beginning.</p>
<p>Needs: Listen to parents, believe what they tell about their children. Do urine tests (glucose) and blood tests (loss of electrolytes; dehydration) even in very young children.</p>	<p>Needs: Give well informed the right diagnosis. Explain about the disease, not only give its name. Give information about patient organisation and recommend strongly to get in contact.</p>	<p>Needs: Care coordination in a multidisciplinary team. This is a metabolic disease with many different health problems involved. Free access to medicines and further treatment.</p>	<p>Needs: A multidisciplinary approach is important, including nephrologist, ophthalmologist, internist in metabolic diseases and if required, an endocrinologist, a social worker and/or neurologist.</p>	<p>Needs: A multi-disciplinary team of experienced specialists working hand in hand in one clinic seeing many patients is the best for all patients.</p>
<p>Ideally: Early diagnosis is crucial. Treatment to slow down the progress of the disease can be given from day 1 is available and has to be prescribed and paid by insurances in all countries.</p>	<p>Ideally: Nephrologic paediatric cooperates with a specialized interdisciplinary center for cystinosis, but stays the main partner of the patient (family). No long stay in the clinic, no examinations that are not necessary.</p>	<p>Ideally: Psychosocial as well as medical care. Openness to new ideas is important, therefore accept patients' solutions in dealing with daily life problems</p>	<p>Ideally: Transition from paediatric to adult care is a precarious process, which is best done in a cystinosis center of expertise. Information on the use of cysteamine is crucial. Surgery: Think of dehydration first and give fluids intravenous all the time while a patient is not allowed to drink.</p>	

Figure 22: cystinosis patient's journey described by ERKNet

Title: Cystinosis, an inherited rare metabolic disease: between available treatments and unmet needs

Abstract: Cystinosis is a rare disease characterized by an intra-lysosomal build-up of cystine in cells. Without any treatment, patients suffer from end-stage renal disease around 6-8 years of age. Several treatment options exist for patients with cystinosis; yet there is no current solution to definitively cure them. And there are still a lot of challenges and unmet needs revolving around cystinosis. Having treatment options does not necessarily mean disease progression stopped, patients perfectly treated, or even treated at all. Nonetheless, researchers, clinicians, healthcare professionals, pharmaceutical companies and patients associations collaborate to bring patients innovative and hopeful solutions. This thesis aims to gather an up to date and consistent review of: the disease, its challenges, and the current and future remedies brought by the cystinosis community as a whole to make patients' lives better.

Keywords: Cystinosis / Cystine / Cysteamine / Fanconi syndrome / Lysosomal storage disease / Autosomal recessive inheritance / Renal transplantation / Rare disease

Titre: La cystinose, une maladie rare métabolique héréditaire: entre traitements disponibles et besoins non satisfaits

Résumé: La cystinose est une maladie rare caractérisée par une accumulation intra-lysosomale de cystine dans les cellules. En l'absence de traitement, les patients souffrent d'une insuffisance rénale terminale vers l'âge de 6 à 8 ans. Plusieurs options thérapeutiques existent pour les patients atteints de cystinose, mais aucune ne peut les guérir définitivement. La cystinose soulève encore de nombreux défis et besoins non satisfaits. Le fait de disposer de traitements ne signifie pas nécessairement que la progression de la maladie est stoppée, que les patients sont parfaitement traités ou même qu'ils sont traités tout court. Néanmoins, les chercheurs, cliniciens, professionnels de santé, entreprises pharmaceutiques et associations de patients collaborent pour apporter aux patients des solutions innovantes et porteuses d'espoir. Cette thèse a pour objectif de dresser un état des lieux actualisé et cohérent de la maladie, de ses défis et des remèdes actuels et futurs apportés par l'ensemble de la communauté de la cystinose pour améliorer la vie des patients.

Mots clés: Cystinose / Cystine / Cysteamine / Syndrome de Fanconi / Maladie de surcharge lysosomale / Transmission autosomique récessive / Transplantation rénale / Maladie rare