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Consensus document

Cystinosis in adult and adolescent patients: Recommendations for the comprehensive care of cystinosis☆

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ABSTRACT

Introduction: Cystinosis is a rare systemic lysosomal storage disease that mainly affects the kidney and the eye. Renal replacement therapy is started in patients with cystinosis during the first decade of life in the absence of treatment. The prognosis of cystinosis depends on early diagnosis and the prompt start of and good compliance with cysteamine treatment. Kidney disease progression, extra-renal complications and shorter life expectancy are more pronounced in patients who do not adhere to treatment.

Objective: The aim of this work was to establish recommendations for the comprehensive care of cystinosis and facilitate patient transition from paediatric to adult medicine, based on clinical experience. The goal is to reduce the impact of the disease and improve prognosis and patient quality of life.

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Methods: Bibliographic research and consensus meetings with a multidisciplinary professional team of clinical experts in cystinosis (T-CiS.bcn group) from 5 hospitals in Barcelona.
Results: This consensus document gathers specific recommendations for the diagnosis, treatment and multidisciplinary care of cystinotic patients in the following areas: nephrology, dialysis, kidney transplantation, ophthalmology, endocrinology, neurology, laboratory, genetic counselling, nursing and pharmacy.
Conclusions: Guidelines for the comprehensive care of cystinosis provide a support tool for health professionals who look after these patients. They are based on the following main pillars: (a) a multidisciplinary approach; (b) appropriate disease monitoring and control of white blood cell (WBC) cystine levels; (c) the importance of adherence to cysteamine treatment; and (d) the promotion of patient self-care by means of disease education programmes. All these recommendations will lead us, in a second phase, to create a coordinated model of transition from paediatric to adult care services which will cover the specific needs of cystinosis.

Cistinosis en pacientes adolescentes y adultos: recomendaciones para la atención integralde la cistinosis

Palabras clave:
Cistinosis
Cisteamina
Síndrome de Fanconi
Cistina intraleucocitaria
Transición
Adherencia

RESUMEN

Introducción: La cistinosis es una enfermedad lisosomal minoritaria de expresión sistémica con especial afectación renal y oftalmológica, en la que los pacientes inician terapia renal sustitutiva en la primera década de la vida en ausencia de tratamiento. El pronóstico de la cistinosis depende del diagnóstico precoz, la pronta instauración del tratamiento con cisteamina y el buen cumplimiento terapéutico. La progresión de la enfermedad renal y de las complicaciones extrarrenales y una menor supervivencia, son más acentuadas en pacientes no adherentes.
Objetivo: El objetivo de este trabajo fue la elaboración de unas recomendaciones para la atención integral de la cistinosis y la transición del adolescente a la medicina del adulto, basadas en la experiencia clínica, con el fin de reducir el impacto de la enfermedad y mejorar la calidad de vida y el pronóstico del paciente.
Método: Búsqueda bibliográfica y reuniones de consenso de un equipo multidisciplinar de expertos en la práctica clínica con pacientes afectos de cistinosis (Grupo T-CiS.bcn), procedentes de 5 hospitales localizados en Barcelona.
Resultados: El documento recoge recomendaciones específicas y necesarias para el diagnóstico, tratamiento y seguimiento multidisciplinar de la cistinosis en las siguientes áreas: nefrología, diálisis, trasplante renal, oftalmología, endocrinología, neurología, laboratorio, consejo genético, enfermería y farmacia.
Conclusiones: Disponer de un documento de referencia para la atención integral de la cistinosis constituye una herramienta de soporte para los profesionales de la salud que asisten a estos pacientes. Los principales pilares en los que se sustenta son: a) el enfoque multidisciplinar, b) la adecuada monitorización de la enfermedad y control de los niveles de cistina intraleucocitarios, c) la importancia de la adherencia al tratamiento con cisteamina y d) la promoción del autocuidado del paciente mediante programas de educación en la enfermedad. Todo ello conducirá, en una segunda fase, a la elaboración de un modelo de transición coordinado entre los servicios de pediatría y de adultos que contemple las necesidades específicas de la cistinosis.

Introduction

Cystinosis is a rare systemic lysosomal storage disease which, if not treated, leads to end-stage kidney failure in the first decade of life.[1] Its natural history has been transformed thanks to the development of kidney transplantation (KTx) in children[2] and the availability of specific treatment with cysteamine, a drug therapy that should be maintained throughout the patient's lifetime.[3] As a consequence, patient survival has increased from the first decade of life to beyond

the fourth decade and cystinosis has passed from paediatrics to adult medicine.[4]

The control of cystinosis is complex owing to its severity and multisystemic nature, and the requirement of treatment with several drugs with a very strict dosage schedule. Early diagnosis, prompt cysteamine administration and treatment adherence influence morbidity and prognosis.[5,6] Nevertheless, adherence to therapy, which is usually good in children, tends to wane in teenagers and adults.[7] Furthermore, when patients reach adult age, they are usually transferred from the paediatric expert centre to a local hospital with limited experience in cystinosis, while the systemic manifestations continue to progress and the disease becomes more complex.[8] This phenomenon is seen in other chronic renal diseases that debut in paediatric patients[9] and highlights the need to implement transition strategies and promote patient self-care.[10]

The current cystinosis count in Spain comprises 56 patients treated and followed up at 22 hospitals. Approximately 50% are adults and 16% adolescents; 57% are kidney transplant recipients.[7]

The working group for the care and transition of cystinosis in Barcelona (T-CiS.bcn) has assembled a group of experts in the disease to establish, as a first step, recommendations for the comprehensive care of cystinosis and the transition of adolescents to adult-care units in our country. This consensus document presents a support tool for health care professionals both involved in and interested in cystinosis. It is focused on reducing disease impact, improving quality of life and prolonging survival, in accordance with the guidelines of the International Society of Nephrology (ISN) and the International Paediatric Nephrology Association (IPNA).[10] At a later date, the T-CiS.bcn group plans to create a coordinated model of transition from paediatric to adult care services which will cover the specific needs of cystinosis.

Etiopathogenesis

Cystinosis is a hereditary autosomal recessive disease caused by mutations with loss of function of the *CTNS* gene (chromosome 17p13), which encodes for cystinosin.[11] Cystinosin is a specific transmembrane protein for the transport of cystine from the lysosome to cell cytoplasm.[12] Its absence causes progressive deposits of intralysosomal cystine, the main diagnostic marker of the disease[1]. Its annual incidence is estimated at 1/100,000–200,000 newborns, while the population prevalence is 1–9/1,000,000.[13] The most frequent mutation in the *CTNS* gene is a deletion of 57 Kb[14] which is also observed in 34% of patients in the Spanish population.[15]

The amino acid cysteine oxidises inside the lysosome and forms cystine. In patients with cystinosis, there is an accumulation of cystine that precipitates in crystal form in all the cells of the organism, particularly in renal and ocular tissue.[16] The increase in the lysosomal concentration of cystine is associated with increased cellular apoptosis, oxidative stress and alterations in the metabolism of glutathione and arachidonic acid.[17–19] Other pathogenic mechanisms involved are inflammatory[20] and "endoplasmic reticulum stress", which finally lead to cell death.[21,22]

Symptoms

Cystinosis is a multisystemic disease[23] with the kidneys and eyes being the first organs to be affected. Three clinical forms have been described: infantile nephropathic cystinosis (OMIM#219800), the most serious subtype, which debuts early on; juvenile nephropathic cystinosis (OMIM#219900), a less severe subtype, which debuts in childhood or later; and adult non-nephropathic cystinosis (OMIM#219750), with exclusively ocular involvement.[24] Nonetheless, in clinical practice, two main subtypes are defined: nephropathic cystinosis that debuts in early childhood with severe Fanconi syndrome (representing 95% of all cases) and late-onset non-nephropathic cystinosis, which appears in young patients or adults with renal and/or ocular involvement (representing <5% of affected patients). In some patients, ocular involvement can precede renal manifestations by several years.[25]

Renal disease

Fanconi syndrome

Typical clinical symptoms include the appearance of severe Fanconi syndrome with evolution to chronic kidney disease (CKD) (Fig. 1). Tubulopathy characteristically becomes evident in the second semester of life after a symptom-free interval.[24] Affected newborns are apparently normal, although it is possible to detect urinary alterations (alkalineurine with glycosuria and/or proteinuria) very early preceding symptoms.[26] Cystinosis is the most frequent cause of inherited Fanconi syndrome[24] and should be considered in the initial differential diagnosis in newborns. Nonetheless, cases have been described of cystinotic patients who debuted with atypical symptoms not suggestive of Fanconi syndrome but of distal tubulopathy, such as nephrogenic diabetes insipidus or Batter syndrome. Thus, the diagnosis of cystinosis should be considered in all newborns with complex tubulopathy, particulary if growth is affected and the patient is anorexic.[1] The differential diagnosis should contemplate the possibility of secondary proximal tubulopathy.[27,28] The severity of Fanconi syndrome associated with cystinosis requires rigorous treatment that is frequently very complex (Table 1).

Chronic kidney disease

After the age of two, if no specific treatment is administered, glomerular involvement progress with a drop in the glomerular filtration rate (GFR) and an increase in plasma creatinine starting at the age of 4 to 6, which evolves to advanced CKD.[1] Concurrently, Fanconi syndrome usually remits and, consequently, it is possible to reduce water/electrolyte supplements (Table 1). In the absence of specific pharmacological treatment (cysteamine), mean age at the onset of end-stage renal disease (ESRD) is 9.2 years. In more contemporary series including patients who received early treatment with cysteamine, there is a significant delay in evolution to ESRD at the age of 13.5 which has been attributed to better patient control by physicians. Furthermore, in cases with very early diagnosis and treatment, there is a growing percentage of patients who remain in predialysis after adolescence.[6]

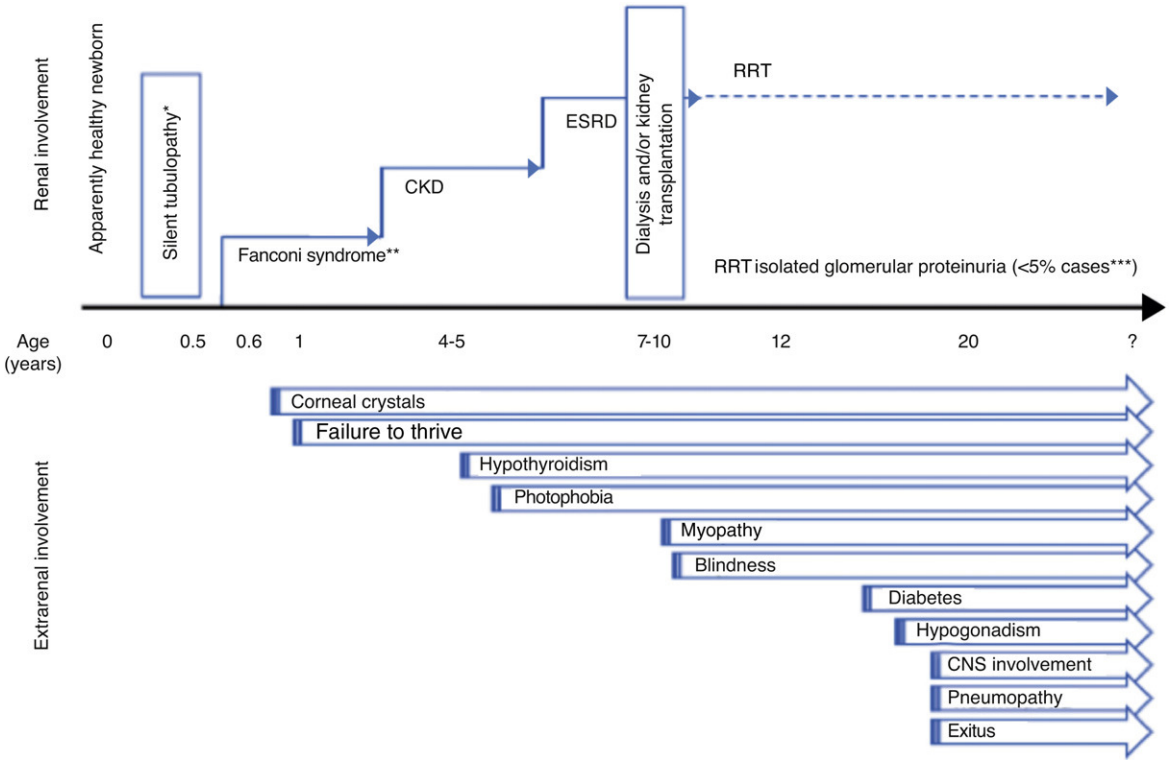

Fig. 1 – Clinical manifestations of cystinosis in patients not treated with cysteamine. CKD: chronic kidney disease, ESRD: end stage renal disease, RRT: renal replacement therapy.

There are also forms of attenuated or late-onset cystinosis that debut in adolescence or in young adults, such as glomerular disease and proteinuria without Fanconi syndrome, although occasionally signs suggestive of proximal tubulopathy are observed. Usually, patients also present ocular manifestations of the disease that can be nearly asymptomatic[25] (Fig. 1).

Although renal biopsy is not necessary for diagnosis, it demonstrates non-specific lesions of glomerulosclerosis and other more characteristic signs such as irregularities on the brush border of proximal tubule cells, swan neck deformity and, occasionally, deposits of cystine crystals and giant multinucleated podocytes.[2,16,24]

Dialysis

The renal replacement therapy (RRT) of choice in cystinosis is the kidney transplantation (KTx) since the disease does not recur in kidney grafts. In many cases, however, the limitation of organs or delayed diagnosis results in the start of dialysis. According to the NAPRTCS register, 1.4% of patients <18 years of age who initiated chronic dialysis had cystinosis.[30] On the other hand, in the European ESPN/ERA-EDTA Registry, 0.9% of patients <20 years of age and 0.1% of patients >20 years with RRT had cystinosis. In Europe, peritoneal dialysis (PD) was the most frequent initial treatment modality (39.6%), followed by preventive KTx (35.1%). Some 17.9% of patients received haemodialysis (HD).[5]

Fanconi syndrome can persist after the start of dialysis, which influences the dietetic prescription for water, patient diet and the possible need to administer other medications such as phosphorus chelates. Although the urinary loss of saline and polyuria usually decrease in advanced CKD, the patient may continue to need water/electrolyte supplements and carnitine (Table 1). On rare occasions, the severity of Fanconi syndrome justifies nephrectomy of the native kidneys.[31] Moreover, many cystinotic patients on dialysis characteristically present extrarenal involvement requiring the integrated intervention of other specialists (see section on extrarenal involvement), which can be a challenge for nephrologists when treating their patients.[32]

Kidney transplantation

As previously stated, the RRT of choice in cystinosis is KTx. Since graft cells do not carry the lysosomal defect, the disease does not recur in the transplanted organ. However, it is possible to observe interstitial deposits of cystine crystals, which represent leukocytes of the recipient and have no pathological significance.[21] Family-donor transplantation is also curative, and heterozygous carriers of the CTNS mutation can be appropriate donors since they do not have the disease.[4,6,33]

Indirect data from cystinotic patients with advanced kidney failure and international registries suggest that preventive kidney transplantation would be beneficial in this disease, particularly when a living donor is available[4] thereby avoiding the need for dialysis.[5] Thus, the indication for kidney transplantation is established when the GFR is <20 ml/min/1.73 m^2, which would be somewhat earlier than in other kidney diseases.[1]

In the United States (USRDS2013), mean age of patients with cystinosis at the first KTx is 13.8 years (range: 2 to 24),

Table 1 – Symptomatic treatment of renal disease in cystinosis.[1,24,29,31]

Therapeutic aims	Treatment
Preserve water balance by replacing losses	Replace water loss according to need (between 1.5 and 6 L/day), either orally or by nasogastric tube or gastrostomy, if needed. Reduce polyuria: oral indomethacin (1–3 mg/kg/day)
Preserve electrolyte balance by replacing losses	Potassium (between 2 and 10 mEq/kg/day) ClNa (1–2 mEq/kg/day, with progressive increase in dosage) Phosphorus (between 1 and 4 g/day)
Neutralise acidosis (maintain normal blood pH and serum bicarbonate between 22 and 24 mEq/L)	Bicarbonate or citrate at an initial dose of 1–2 mEq/kg/day, with progressive increase in dosage
Nutritional support	Nutritional assessment with appropriate caloric supplementation according to age and kidney function
Treatment of bone mineral disease	Cholecalciferol Calcium supplements Active vitamin D (1 Alpha-vitamin D, Calcitriol, Paricalcitol, others) Growth hormone (if indicated)
Others	Carnitine[29] (100 mg/kg/día) ACEi/ARB antiproteinuric agents (assess tolerance)

ACEi/ARB: inhibitors of the renin-angiotensin system.

which has not changed in recent decades; 32.4% underwent preventive KTx.[34] Similarly data from the European Registry (ESPN/ERA-EDTA Registry) show a similar percentage of 35.1% predialysis transplantations, a much higher percentage than in other nephropathies (17.1%).[5] Eighty-five percent of all the cystinotic patients in RRT were kidney transplant recipients. Regarding the type of donor, 54% of patients in the US received a living and 46% a deceased donor organ.[34] Similarly, in Europe 48.9% received a living donor transplant.[5]

It is worthy of mention that the duration of functioning kidney grafts in cystinotic patients is longer than that observed in the population of recipients transplanted for other causes.[5,35]

Extrarenal disease

The longer survival and better prognosis of patients with cystinosis have resulted in better understanding of the multiple organ involvement in this disease[4,6,32,36] (Fig. 1).

Ocular involvement

Eye involvement is intrinsic to cystinosis. The presence of cystine crystals in the cornea is a diagnostic criterion for this disease,[37] although its absence before the age of 12 months may not rule it out.[1]

Cystine deposits in the cornea are one of the earliest manifestations of cystinosis (Fig. 1). Although no crystals are present at birth, they can be observed in children who are only a few months old.[1] Initially, they are deposited in the superficial layers of the peripheral cornea, but progressively begin to affect all the layers and entire extension of the cornea. If left untreated, corneal crystal deposits progress inexorably, increasing with age, resulting in photophobia, which can be quite incapacitating, and in abnormal corneal sensitivity. In time, this condition leads to recurrent corneal erosions and stromal oedema, which can reduce visual acuity. Reports also exist of calcium deposition in Bowman's membrane or band keratopathy, which affect vision when situated in the visual axis.[37]

Crystals are also deposited in other ocular structures such us the conjunctiva, anterior chamber, iris, ciliary body, choroid and retina. Retinal involvement causes degeneration of the photoreceptors, mainly the rods, thereby altering the peripheral visual field and night vision, although central vision may also be reduced. Less frequently, there have been reports of posterior synechiae, adherence of the iris to the anterior lens capsule and neovascularisation of the peripheral cornea.[38,39] Furthermore, tear production is reduced, causing dry eye, and neuro-ophthalmological manifestations (papilledema and ophthalmoplegia) are observed secondary to the increased intracranial pressure reported in this disease.[4] In late-onset disease, the presence of crystals might not be detected until adulthood.[25]

Growth and development: mineral-bone involvement

Failure to thrive is a classic clinical symptom of cystinosis and frequently is the reason for an early consultation.[36] The underlying mechanism is multifactorial, although it is related to Fanconi syndrome severity. The concurrence of metabolic acidosis, hyponutrition, increased gastrointestinal and renal losses and CKD lead to delayed growth that can be very severe.[40,41] Similarly, patients present endocrine alterations (see endocrine involvement section) and, infrequently, primary growth hormone (GH) deficiency.[42]

Patients with inadequate treatments usually have shorter stature.[36] Classically, the adult height reported in patients with suboptimal treatment is 144 cm and weight 45 kg (25 cm and 25 kg below the normal population average, respectively).[4] The most recent series with better therapeutic control reported less retarded growth[8] and a favourable impact of treatment on growth regulation mechanisms.[43] Nevertheless, nowadays 27% of transplanted cystinotic patients and 44% of those on dialysis continue to be shorter than average.[5]

Early GH administration improves height and weight, although the therapeutic response is usually lower than that observed in CKD due to other causes, despite optimum disease control. GH is an essential therapeutic tool in this disease, for its impact on longitudinal growth and its anabolic effect.[40,44] Patients with cystinosis develop a characteristic metabolic bone disease caused by different factors: bone deposits of cystine crystals, mineral deficiency, renal rickets[24] and CKD *per se*.[45] Bone anomalies attributed to copper deficiency, possibly secondary to Fanconi syndrome have also been described.[46] It is therefore common to detect osteopenia, especially in trans-

plant recipients, related also to other endocrine alterations of the disease (see endocrine involvement section) and potentially to the treatment.[23,47] Some patients have bone fragility and a higher risk of fractures.[32]

Endocrine involvement

Endocrine manifestations are caused by destruction of the affected glands due to cystine deposits; their incidence and age at appearance are associated with the establishment of specific treatment with cysteamine.[43]

Primary hypothyroidism is the most frequent endocrine complication;[23] it is progressive and requires chronic treatment with levothyroxine.[1,4] Diabetes mellitus (DM) is characterised by a progressive alteration in insulin secretion,[48] with negative immunology, and requires treatment with insulin.[2] It is observed in transplant recipients who receive corticosteroids.[23] In males, cystinosis causes primary hypogonadism and infertility is a constant.[4,49] In females, however, neither hypogonadism nor infertility are prevalent, and affected patients can thus have children,[50] although the risk of prematurity is increased.[51]

Cardiovascular involvement

The appearance of dyslipidemia and vascular calcification due to cystinosis and CKD are considered increased cardiovascular risk factors.[23,32,41] 42% of patients develop arterial hypertension, usually post-transplantation. Aortic aneurysms and coronary vessels involvement, as well as cardiomyopathy associated with cystine crystals deposits in the myocardium have also been reported.[36] In adult patients, screening for ischaemic heart disease is recommended.[4]

Neurological involvement

Cystinosis is associated with alterations in cerebral structure and increased cystine levels in different areas of the nervous system and muscle tissue.[4,6,32,52] In general, neurological complications worsen the prognosis of the disease:

- Progressive ischaemic myopathy[4,32,53] is predominantly distal and begins in the hands; loss of muscle mass is also observed with later ventilator capacity impairment and swallowing difficulties. Some authors attribute muscle weakness in these patients to carnitine deficiency.[24,28,29]
- Central nervous system (CNS) involvement[4,31] is mainly observed in patients with suboptimal treatment with cysteamine:
  - Acute presentation: epilepsy, stroke, encephalopathy, cephalalgia[54–57]
  - Subacute/progressive presentation: intracranial hypertension, cerebral atrophy, ataxia, pyramidalism, gait disorders, basal and periventricular lymph node calcifications, demyelination of white matter, mental deterioration[58–66]
- Neurocognitive alterations:[67–73] in cystinotic patients, a specific profile of alterations in visual-motor integration, visual memory, maintained attention, planning, motor processing speed and arithmetic calculation have been described. Consequently, they account for a significant incidence of social difficulties that could explain the behavioural phenotype in some patients. Intelligence is usually normal.

Early detection of neurological complications in cystinosis facilitates better therapeutic strategies, reduces the number of hospitalisations and improves quality of life. The participation of a neurologist will help to evaluate the functional capacity of patients and detect earlier the neurological manifestations that can affect autonomy in basic daily life activities.[8,31,32,55]

Miscellaneous

The ubiquity of cystinosis is demonstrated by its non-specific symptoms e.g. gastrointestinal and other disorders such as heat intolerance and hypophoresis. Similarly, the systemic nature of the disease explains the progressive appearance of other clinical symptoms secondary to the deposition of cystine crystals in different organs and systems, as detailed below (Fig. 1):

- Digestive system[74]:
  - Nausea, vomiting, epigastralgia, anorexia
  - Increased gastrin secretion (associated with taking cysteamine)
  - Decreased salivation
  - Mechanical swallowing difficulties
  - Delayed gastric emptying and intestinal and intestinal dysmotility
  - Intestinal pseudo-obstruction
  - Intestinal inflammatory disease
- Liver[32,75]:
  - Regenerative nodular hyperplasia without liver failure
  - Non-cirrhotic portal hypertension with hypersplenism
  - Cholestasis
  - Hypercholesterolemia
- Skin[1,76]:
  - Hypopigmentation of skin and hair due to altered melanogenesis
  - Altered sweating and intolerance to heat
- Bone marrow[4]:
  - Anaemia
  - Coagulopathy due to dysfunctional platelets

Diagnosis

The clinical diagnosis of cystinosis is symptom-based and is confirmed by biochemical and molecular diagnosis.

Clinical diagnosis

Guiding signs are early-onset of severe Fanconi syndrome and the detection of corneal crystals. As the disease progresses, systemic involvement may be observed (Fig. 1). However, in patients with less severe forms, renal involvement is restricted to proteinuria and CKD. Occasionally, corneal crystals in adult patients with CKD of unknown aetiology lead to the diagnosis of cystinosis.[25] Kidney biopsy, while not a requirement for the diagnosis of cystinosis, can be useful in these atypical presentations.[2,16,24,32]

Table 2 – Biochemical diagnosis and WBC cystine level monitoring. Molecular diagnosis (www.orpha.net).

Requirements for WBC cystine level monitoring[77–79]	
Sampling conditions	No fasting required In treated patients, blood extraction should be made 6 h post-cysteamine dose Collect within lithium or sodium heparin tube Ship immediately to the laboratory: it should be processed into 24 hours post-sampling Keep at room temperature
Minimum volume	For patients <10 kg body weight: 6 mL blood For patients ≥10 kg body weight: 10 mL blood
RECOMMENDATIONS for monitoring WBC cystine levels	At the start of Cystagon® treatment Monthly after dose adjustments Every 6 months in stable patients Increase frequency in cases of significant clinical changes (Transplantation and Dialysis)
Reference Laboratory in Spain Hospital Clínic de Barcelona Servicio de Bioquímica y Genética Molecular. Sección de Errores Congénitos del Metabolismo Dra. Judit García Villoria: jugarcia@clinic.ub.es Tfn. 93 227 56 00 Ext. 7585 C/ Mejía Lequerica s/n. Edificio Helios III. Planta baja. 08028 Barcelona, Spain.	
Requirements for the molecular diagnosis of *CTNS* gene[12,13,15,80]	
Genetic testing of patient and family Sample	2–3 mL blood in EDTA at room temperature DNA at room temperature
Prenatal testing Sample	DNA from cultured amniocytes or chorionic villi sampling
Prior identification of the disease-causing mutations in parents and in index case Previous appointment with the laboratory is essential	
Reference Laboratory in Spain Hospital Clínic de Barcelona Servicio de Bioquímica y Genética Molecular. Sección de Errores Congénitos del Metabolismo Dra. Mª Josep Coll: mjcoll@clinic.ub.es Tfn. 93 227 9341 C/ Mejía Lequerica s/n. Edificio Helios III. Planta baja. 08028 Barcelona, Spain.	

General biochemical diagnosis

This diagnosis is based on the detection of water/electrolyte disorders, affected acid-base balance and eventually renal function, which are all prototypical of Fanconi syndrome.[24,28]

Specific biochemical diagnosis

This involves the detection of elevated white blood cells (WBC) cystine levels.[77] Currently High Performance Liquid Chromatography–Tandem Mass Spectrometry (HPLC-MS/MS) in granulocytes is used as it is a more sensitive technique.[78,79]

The reference values are:

- healthy individual: ≤0.5 nmol 1/2 cystine/mg protein (values >0.5 may have diagnostic significance, and it is recommended to repeat the determination)
- affected individual without treatment: >1 nmol 1/2 cystine/mg protein (usually >2)
- individual treated with good therapeutic control: ≤1 nmol 1/2 cystine/mg protein

Normal WBC cystine levels in newborns do not completely rule out the diagnosis. Therefore, in cases where cystinosis is highly suspected, a second test is recommended 3–6 months after the first study when the results are not conclusive[79] (Table 2).

Molecular diagnosis

Cystinosis is confirmed by the detection of homozygous or compound heterozygous mutations in the *CTNS* gene. More than 100 different mutations have been reported and the most frequent one is the ~57 kb deletion affecting the first 10 exons, especially in patients of Northern European descent. Specific mutations turn into an absence of protein or a probably non-functional truncated protein[11,12,14,15,80] (Table 2).

Genetic counselling

Since cystinosis is an autosomal recessive disease, the probability of a family with one affected child having another with cystinosis is 25%.[81] In this case, genetic counselling includes information on prenatal diagnostic techniques and embryo

Table 3 – Specific treatment with cysteamine.

	Oral Cysteamine – Cystagon®[31,47,92,93,94,102]	
Dosage		
By age	**Children ≤12 years**	**Patients >12 years**
Recommended dosage	**by body surface area** (g/m²/day)	**if weight > 50 Kg**
(Dosage should be divided 4 times daily)	**1.30 g/m²/day**	**2 g/day**
Starting dosage	1/4 to 1/6 of the recommended dosage Increase gradually over 4–6 weeks to avoid intolerance**	
Dosage adjustments	Raise if adequate tolerance and WB C cystine level is greater than **> 1 nmol ½ cystine/mg protein**	
Maximum dosage	**1.95 g/m²**/day ***Overdosing*** *is not recommended since it does not improve the prognosis and is associated with adverse effects*[47]	
Renal insufficiency	No dose adjustment required	
RECOMMENDATIONS for appropriate dosage	Treatment should be initiated under the supervision of a physician experienced in the treatment of cystinosis **4 doses per day; every 6 hours; night dose included**	
	Adjust the dose according to WBC cystine levels	
	Hard capsules should not be administered to children under the age of 6 years owing to risk of aspiration	
	If needed, open the capsules and sprinkle the content on food	
	Cysteamine powder could be mixed with milk, potatoes and other starch-based products. Avoid acidic drinks.	
	CYSTAGON® should be restarted after renal transplant to prevent non-renal complications	
Side effects	Gastrointestinal disorders due to gastric acid hypersecretion	
	RECOMMENDATIONS for improving gastrointestinal tolerability:	
	Concomitant administration of proton pump inhibitors[102]	
	Administer with meals or immediately afterwards. Intake is recommended with food such as milk, potatoes or other starchy foods[92–94]	
	Characteristic body odour and halitosis *RECOMMENDATIONS for improving halitosis: mentholated pills*[31]	
	Other adverse reactions refer to SMPC[92–94]	
Drug interactions	No interaction studies have been conducted	
	Can be administered in conjunction with electrolytic or mineral supplements, vitamin D analogues, tyrosine or immunosuppressive drugs	
	Cysteamine eye drops[37–39,105–109]	
Eye drops	0.55% cysteamine solution *(see Annex 1)*	
Dose	**1 drop/eye**	
Dosage	**10–12 instillations/day**	

selection.[82,83] The probability of a woman with cystinosis having an affected child is very low, except in consanguineous families or endogamous populations. Males with cystinosis are universally sterile.[49]

Genetic counselling usually includes information on patient associations[84–86] and institutional strategies in rare diseases.[87]

Treatment

Symptomatic treatment of kidney involvement

The aim of treatment (Table 1 & Annex 1) is to control Fanconi syndrome, its complications and other factors involved in kidney failure progression.[24–28] In ESRD, promoting KTx is a priority. Regardless of kidney involvement, all patients should receive specific treatment with cysteamine for the prevention and therapeutic control of the systemic disease.

Treatment of CKD should follow international guidelines.[88–90] In transplanted patients, minimising or avoiding corticosteroids use is recommended.[23]

Specific treatment with cysteamine

Oral cysteamine

The specific treatment for all clinical forms of cystinosis is oral cysteamine. Cysteamine depletes lysosomal cystine content

Table 4 – Recommendations for improving treatment compliance.[7,9,10,114–119]

Identify risk factors that affect adherence and apply corrective measures when possible:
- Intrinsic patient and socio-economic factors
- Disease-related factors
- Treatment-related factors
- Healthcare system organisation barriers

Identify and assign a "Patient health Coordinator"

Promote patient education and treatment support:
- Implement disease education programmes
- Establish treatment programmes: easy to follow with support measures for compliance
- Use questionnaires to detect non-compliance
- Follow-up of appointments and absences

Develop patient support programmes involving family members, friends and patient associations

Create a multidisciplinary medical team

Implement protocols for transition to adult care

by forming disulphide cysteine–cysteamine complexes able to exit the lysosomes by means of the alternative lysine channel, and the remaining cysteine via a cysteine carrier.[3,19,91]

The first specific pharmacological treatment for cystinosis is Cystagon® (oral cysteamine bitartrate in hard capsules), the only authorised therapy in Spain[92–94]. A new formula in hard gastro-resistant capsules has recently been approved for cysteamine.[93–96]

Therapeutic benefits

Oral cysteamine should be initiated at the time of diagnosis and continued lifelong. When compliance is consistent, cysteamine is able to deplete up to 95% of cellular cystine deposits.[62] The reduction in these deposits correlates with cystinosis severity.[32] It has been demonstrated that cysteamine prolongs the life of the patient, while delaying kidney disease progression and the need for renal replacement therapy.[5,97] Similarly, it reduces the severity and frequency of extrarenal complications.[32] Prognosis of the disease is directly related to early treatment and its duration. Even when cystinosis diagnosis is delayed, cysteamine has demonstrated clinical benefits.[4,6,98] Although Fanconi syndrome is not usually reversible with cysteamine,[19] in some isolated cases of prenatal diagnosis the beginning of cysteamine therapy within the first weeks of life prevented the appearance of tubulopathy.[99,100]

Cystagon®: dosage, administration and treatment monitoring

Treatment is based on the depletion of lysosomal cystine content which, in clinical practice, means the reduction of WBC cystine levels, with an optimal therapeutic goal <1 nmol hemicystine/mg of protein. The decrease in those WBC cysteine levels correlates with plasma cysteamine concentrations for the 6 hours following Cystagon® dose, being minimum at ~2 h after the drug is taken and returning to baseline (pre-dose) 6 h later. This explains the need to take the drug every 6 h, overnight dose included[101,102] (Table 3).

Monitoring of WBC cysteine levels at the start of treatment and monthly after changes in the prescribed dosage is recommended. In patients with maintained cystine levels, follow-up controls are recommended every 6 months. Similarly, in an individualised manner, the frequency of monitoring should be increased in case of significant clinical changes such as KTx and dialysis[77,78,79] (Table 2).

Oral treatment in special situations

Chronic kidney disease, dialysis and transplantation

Since there is no correlation between GFR and plasma cysteamine levels, it is not necessary to adjust the dosage to renal function; instead, the prescribed dosage should be adjusted to the quantification of WBC cystine levels. Adjustments for Fanconi syndrome are also unnecessary.[6,103]

Pregnancy and breastfeeding

Although data is insufficient, reproductive toxicity and teratogenic effects of cysteamine have been observed in animals.[104] Its use is therefore contraindicated during pregnancy, particularly in the first trimester. Family planning is recommended in women of childbearing age. Furthermore, cysteamine administration should be avoided during breastfeeding.

Cysteamine eye drops

Specific treatment of ocular involvement in cystinosis requires, in addition to oral cysteamine, the use of cysteamine eye drops. The ophthalmological therapeutic strategy[32,37] makes a distinction between:

Corneal involvement

Cystine crystal deposits should be treated with topical cysteamine since the cornea is an avascular structure and, consequently, oral medication is not effective for the cornea.[37,38,105,106] The recommended prescription is shown in Table 3. Viscous formulae are being developed to achieve longer contact of cysteamine with the ocular surface and be able to reduce the frequency of instillations with equal efficacy.[107,108]

Involvement of non-corneal structures

Oral cysteamine is effective in the retina and other ocular structures. The incidence of retinopathies has decreased with the systemic use of cysteamine. The frequency and severity of non-corneal manifestations are directly related to compliance with oral cysteamine treatment, and the risk of important vision loss may arise if systemic treatment is not correctly followed.[39,109]

Compliance with specific cysteamine treatment

The World Health Organization (WHO) defines compliance as the degree to which patient behaviour follows the recommendations of medical professionals.[110]

The impact of non-adherence in cystinosis results in poorer prognosis and faster progression of the renal and extrarenal

Table 5 – Recommendations for follow-up of patients on renal replacement therapy (RRT): dialysis (D) and transplantation (TxR).

Recommendations for dialysis[6,103]
Promote preventive KTx as an initial method of RRT in patients with advanced CKD
Monitor residual urine volume and urinary saline loss to adapt the dialysis prescription and avoid excessive ultrafiltration
Maintain the general treatment of Fanconi syndrome and adapt the diet in an individual manner
Carefully monitor extrarenal involvement on a multidisciplinary basis
Oral and ophthalmological cysteamine treatment must be maintained
Cysteamine dosage should not be adjusted to glomerular filtration rate (see Specific Treatment with Cysteamine section)
Recommendations for kidney transplantation[4–6,33,88–90]
Prior to waiting list inclusion
Promote preventive kidney transplantation when the glomerular filtrate ≤20 mL/min/1.73 m^2
Living or deceased donor
Evaluate the associated Fanconi syndrome (residual diuresis – can be very high – saline loss, rickets, tubular acidosis, carnitine deficiency)
Monitor WBC cystine levels and optimise treatment with cysteamine (oral and ophthalmological)
Assess possible systemic involvement and its impact on the transplant (hypothyroidism, diabetes, cardiovascular disease, bone disease, swallowing disorders)
Prescribe fluids and individualised diet. Assess phosphate, potassium, bicarbonate and carnitine supplement requirements
Pre-transplant and peri-transplant
Avoid volume depletion before and during surgery (intensive endovenous fluid therapy to guarantee normovolaemia, including potassium and bicarbonate supplements)
Immunosuppression according to hospital protocol
Temporary suspension of cysteamine treatment
Immediately post-transplant
Administer fluid therapy and sufficient electrolytes to maintain adequate water/electrolyte balance and good control of residual Fanconi syndrome
Monitor the possible appearance of diabetes.
Immunosuppression therapy according to hospital protocol
Continued post-transplant care
Reintroduce cysteamine once the patient and graft are stable, approximately 3–4 weeks post-transplantation, at increasing doses up to therapeutic doses
Monitor WBC cystine levels
Immunosuppression following hospital protocol; promote reduction in and/or suspension of corticosteroids
Controls and follow-up in accordance with recommendations and clinical guidelines
Maintain ophthalmological treatment with cysteamine and stimulate treatment compliance
Assess possible systemic involvement and its impact on transplantation. Promote and standardise a multidisciplinary health care plan for cystinosis
In any clinical situation, it is necessary to administer specific cystinosis treatment with oral cysteamine to maintain recommended WBC cystine levels <1 nmol hemicystine/mg protein and cysteamine eye drops to eliminate corneal deposits (see Table 3).

Table 6 – Recommendations for ophthalmological follow-up.[4,37–39,105–109,120]

Test	Ocular structure	Frequency	Observations
Slit lamp biomicroscopy	Study of the cornea and rest of anterior segment	Annual	
Intraocular pressure measurement	Rule out ocular hypertension	Annual	
Dilated fundus examination	Assess optic disc and retinal pigmentation	Annual In patients with GH, do a baseline assessment and after 4 months to detect intracranial hypertension[120]	Urgent: if the patient reports severe loss of VA (uncommon)
Photopic and scotopic ERG	Functionality of rods and cones	Only if patient reports altered night vision or abnormal retinal examination	
Equipment	Slit lamp* Tonometer Indirect ophthalmoscope		
In any clinical situation, specific cystinosis treatment is required with oral cysteamine to maintain recommended WBC cystine levels <1 nmol hemicystine/mg protein and cysteamine eye drops to eliminate corneal deposits (See Table 3).			

ERG: electroretinogram; GH: growth hormone; VA: visual acuity.

* Very sensitive for diagnosing cystine crystals in the cornea, but less useful for patient follow-up since the quantification of crystals is rather subjective. It is therefore interesting to record detailed data at each examination on the distribution of crystals in the cornea, specifying whether the deposition is only peripheral or diffuse and whether they are located in the epithelium, stroma and/or endothelium.

Table 7 – Recommendations for the follow-up and treatment of endocrine system involvement.[4,5,32,48,49,121]

Disorder	Complementary studies	Frequency	Treatment	Observations
Hypothyroidism	TSH, T4L, Anti-thyroid Ab/Imaging study not necessary	At diagnosis	Levothyroxine	Initiate treatment when TSH > 10 mIU/L/if there are symptoms, consider initiating with TSH, 5–10 mIU/L
	TSH, T4L	Routine follow-up: Quarterly for dosage adjustments/annual, if TSH is normal		
Diabetes Mellitus	Glycaemia, HbA1c (optional: c-peptide) If symptoms of polyuria-polydypsia: laboratory tests with ionogram, venous blood gases and ketonuria	Diagnosis	Insulin	If pancreatic reserve is sufficient, consider single daily dose of slow-release insulin
	Glycaemia, HbA1c	Quarterly or biannual follow-up, according to clinical criteria/annual, if no symptoms		
	Lipid profile: total cholesterol, LDL, HDL and TG	Annual	Dyslipidaemia treatment	
	Funduscopy	Annual	According to ophthalmologist criteria	
	Pain and vibration sensitivity	Annual	Education to prevent lesions	
	Examination feet and pulse	Annual		
Impaired longitudinal growth	Nutritional assessment	According to clinical criteria	Optimise nutrition	Consider supplements and referral to nutritionist
	Height and weight	At each visit		Until bone maturity
	See Fanconi syndrom section		Treatment of Fanconi syndrome	
	Bone age	Diagnosis	r-GH	In pubescent patients, rule out hypogonadism/in transplant recipients, consider withdrawal or reduction of corticosteroids
	GH, IGF-1, IGFBP-3 If no kidney failure: GH secretion studies			
	Bone age, IGF-1	Annual follow-up		
	Funduscopy	Before initiating GH and after 3–4 months under treatment		Intracranial hypertension secondary to GH usually occurs at the start of treatment (mean: 3–4 months)
		Urgent if headache or reduced vision		
	Calcium, phosphorus, alkaline phosphatase, 25OH·D3, PTH	Annual	Vitamin D, if deficiency Calcitriol, if kidney failure	Rule out rickets and vitamin D nutritional deficiency
	Bone mineral density	In adulthood; to be assessed according to results.	If there is osteoporosis, consider specific treatment	

Table 7 – (*Continued*)

Disorder	Complementary studies	Frequency	Treatment	Observations
Hypogonadism	Physical exam: sexual maturation and secondary sexual characteristics	At each visit		During puberty period until complete maturity
	Testosterone, SHBG, LH, FSH + assessment of thyroid function (see above)	Diagnosis	Daily testosterone replacement therapy (TRT): Topical (if panic to injections), or IM (if compliance problems)	If low testosterone with normal LH and FSH levels: MRI of pituitary
	T, LH, FSH	Annual follow-up		
Fertility	Semen analysis	Diagnosis		Infertility is a constant feature in affected males
	Consider high-risk pregnancy			Suspend oral cysteamine during gestation

In any clinical situation, specific cystinosis treatment is required with oral cysteamine treatment to maintain recommended WBC cystine levels <1 nmol hemicystine/mg protein and topical cysteamine to eliminate corneal deposits.

25OHD3: 25-hydroxycholecalciferol (calcifediol); FSH: follicle-stimulating hormone; GH: growth hormone; HbA1c: glycated haemoglobin; IGF-1: insulin-like growth factor 1; IGFBP3: insulin-like growth factor-binding protein 3; LH: luteinising hormone; PTH: parathyroid hormone; rGH: recombinant growth hormone; SHBG: sex hormone-binding globulin; T: testosterone; T4: free thyroxine; TG: triglycerides; TSH: thyroid-stimulating hormone.

disease in patients who are non-compliant compared with those who are.[5,6,97]

Information on adherence in patients with cystinosis is limited, although monitoring WBC cystine levels is able to detect non-compliant patients.[77,79] Other studies have confirmed adequate adherence to Cystagon® in children patients which wanes significantly in adolescents and adults.[7,8] Nonetheless, in groups of highly motivated patients, only 8% had compliance problems.[111]

In cystinosis, risk factors for non-compliance with cysteamine therapy include: dosage schedules, problems with tolerance, side effects and the requirements of several medications for the control of the clinical manifestations of the disease. Moreover, other risk factors which are not exclusive to cystinosis are: limited knowledge of the disease, lack of motivation, inadequate transition of patients to adult care units and impact of the disease on quality of life.[7,9,10]

Nevertheless, suboptimal treatment compliance is not a phenomenon restricted to cystinosis. Recent studies report that 52 to 67% of adult kidney transplant recipients do not correctly follow prescribed immunosuppressant treatment, which increases the probability of graft loss.[112,113] These percentages are similar to those published in patients with cystinosis in our population,[7] which may indicate the coexistence of scenarios in common with CKD. Therefore, in order to improve adherence in cystinotic patients, the recommended strategy is to correct risk factors for non-compliance and promote patient self-care, similar to the strategies used successfully in adult kidney transplant recipients[114–119] (Table 4).

Recommendations for the follow-up and treatment of patients with cystinosis

T-CiS.bcn group members, after an exhaustive review of medical literature and based on our clinical practice with patients, have stablished recommendations for the multidisciplinary care and connected transition from paediatric to adult-care units in cystinosis. Our aim was to provide support tools and medical advice to health care professionals involved and interested in the care of cystinosis.

These recommendations are presented in Tables 4–8.

Table 8 – Recommendations for the follow-up and treatment of neurological involvement.[4,52–73,122–126]

Disorder	Evaluation	Complementary studies	Frequency	Treatment	Observations
Motor functions of the skeletal muscles[4,52,53]	Degree of muscle atrophy/disease progression/degree of disability	MRC scale	Annual	Rehabilitation	Use validate instruments
		Quantitative determinations of hand muscle strength (Jamar dynamometer, Martin vigorimeter and Jamar Hydraulic Pinch Gauge)	Annual		
		Electromyography	According to clinical criteria		
		Muscle MRI	According to clinical criteria		
		Muscle biopsy	According to clinical criteria		
Orofacial motor function (language) and swallowing[58,122,123]	Facial and bulbar muscles: strength and range of movement of lips, tongue, soft palate, jaw and facial muscles in phonation, articulation, swallowing, breathing and expressions	Focused physical examination	Annual	Reeducation if early signs of dysphagia are detected to prevent bronchoaspirates	
		Video fluoroscopy	According to clinical criteria		Objective: to asses different phases of swallowing and movement of food bolus within the oral cavity and its passage through the esophagus
Respiratory muscle function[124]	Presence of dyspnoea, apnoea and/or snoring during sleep, morning headaches, daytime hypersomnia, decreased coughing capacity or increased anomalies in expectoration	Spirometry	Annual	Symptomatic respiratory physiotherapy, ventilatory support (CPAP/BIPAP)	Especially in patients with swallowing disorders, risk of bronchoaspirtion or who present symptoms of neuromuscular respiratory insufficiency
		Oxygen saturation Arterial blood gas	Annual		
		Polysomnography	Annual		
Central nervous system[54–57,59–68,125,126]	Signs of involvement (headache, episodes of unconsciousness, poor school performance, decline in cognitive functions, behavioural alterations, etc.)	Focused physical examination Neurophysiological studies Neuroimaging	Annual	Directed to underlying disorder	Complementary tests if anomalies are detected
			According to clinical criteria According to clinical criteria		
Neurocognitive alterations[69–73]	Neuropsychological examination	Specific evaluation questionnaires for overall cognitive performance, attention and executive functions, language, memory; perceptive, visuospatial and visuoconstructive functions; voluntary cognitive motor control	Annual	Directed to underlying disorder	Adapted to patient's age (school children and adults)

In any clinical situation, specific cystinosis treatment is required with oral cysteamine treatment to maintain recommended WBC cystine levels <1 nmol hemicystine/mg protein and topical cysteamine to eliminate corneal deposits.

MRI: magnetic resonance imaging, CPAP: Continuous Positive Airway Pressure, BIPAP: biphasic positive airway pressure.

Conflict of interest

The authors have no conflicts of interest to declare.

ANNEX 1a.

ANNEX 1.a – Supplements, drugs and pharmaceutical formulations prescribed in cystinosis

Drug	Brand name/Product	Content
	Alkaline supplements	
Sodium bicarbonate	Sodium bicarbonate Torres Muñoz 500mg (30 cap.)	500 mg/comp.
	Sodium bicarbonate Torres Muñoz 60 g; 200 g; 750 g (powder)	
	Sodium bicarbonate Serra 180 g (powder)	
	Sodium bicarbonate Viviar 210 g; 250 g; 500 g (powder)	
	Sodium bicarbonate NM 1 g; 2 g (sachet)	1 g/sachet; 2 g/sachet
	*Sodium bicarbonate 1M (8,4%) solución oral	1 mEq/mL
Sodium citrate	*Bicitra oral solution	1 mEq Bicarbonate/mL; 1 mEq Na/mL; 0.5 mmol citrate/mL
Potassium citrate	*Polycitra oral solution	2 mEq Bicarbonate; 1 mEq Na/mL; 1 mEq K/mL; 1 mmol Citrate/mL
	*Polycitra LC with phosphrous-oral solution	2 mEq Bicarbonate; 1 mEq Na/mL; 1 mEq K/mL; 1 mmol Citrate/mL; 0.6 mmol P/mL
	Potassium supplements	
Potassium ascorbate	Boi-K (20 effervescents tablets)	1 mEq K/tablet
	Bok-K Aspártico (20 effervescents tablets)	25 mEq K/tablet
Potassium chloride	Potasion 600 mg (60 cap.s)	8 mEq K/tablet
Potassium glucoheptonate	Potasion 1,32 g/5 mL (125 mL; 250 mL)	1 mEq K/mL
	Phosphorus supplements	
Sodium Phosphate	*Phosphorus oral solution or Joulie Solution	1 mmol P/ml (30.9 mg P/ml)
	Phosphate Sandoz 500mg (100 cap.)	16.1 mmol P/comp (500 mg P/comp.)
	Sodium Phosphate monobase NM (100 sachets)	26 mmol P/sobre (800 mg P/sachet)
	*Polycitra LC with phosphrous-oral solution	2 mEq Bicarbonate; 1 mEq Na/mL; 1 mEq K/mL; 1 mmol Citrate/mL; 0.6 mmol P/mL)
	Others	
Carnitine	Carnicor 1.5 g/5 mL (40 mLoral solution)	300 mg/mL carnitine
	Carnicor 1 g drinkable vials (10 mL)	100 mg/mL carnitine
	Secabiol 300 mg/mL (40 mL oral solution)	300 mg/mL carnitine
Indomethacin	Artinovo 25 mg (30 cap.)	25 mg indomethacin
	Flogoter 25 mg (40 cap.)	25 mg indomethacin
	Inacid 25 mg (30 cap.)	25 mg indomethacin
	Indonilo 25 mg (24 cap.)	25 mg indomethacin
	*Indomethacin 2 mg/mL oral solution	2 mg indomethacin
Cysteamine	*Cysteamine 0,55% eye drop solution	0.55% cysteamine

cap.: capsules, *: magistral formulation.

Annex 1.b – Supplements, drugs and pharmaceutical formulations prescribed in cystinosis

Compounded formulations

Liquid formulation	Component	Amount
Sodium bicarbonate 1M (8.4%) oral solution[a]	Sodium bicarbonate	8.4 g
	Sterile distilled water (qs)	100 mL
Bicitra oral solution[b]	Sodium, citrate $2H_2O$ (Tri-)	10 g
	Monohydrated citric acid	6.7 g
	Simple syrup with preservatives	50 mL
	Sterile distilled water	40 mL
Polycitra oral solution[b]	Potassium, citrate H_2O (Tri-)	11 g
	Sodium, citrate $2H_2O$ (Tri-)	10 g
	Monohydrate citric acid	6.7 g
	Simple syrup with preservatives	50 mL
	Sterile distilled water	38 mL
Polycitra LC with phosphorus, oral solution[c]	Sodium hydrogenophosphate-12	1.4 g
	Phosphoric acid 85%	1.4 mL
	Sterile distilled water	32 mL
	Potassium, citrate H_2O	11 g
	Sodium, citrate	10 g
	Monohydrate citric acid	6.7 g
	Simple syrup (qs)	100 mL
	Orange extract	1 drop
Indomethacin 2 mg/mL oral solution[d,e,f,g]	Indomethacin	0.2 g
	Ethyl alcohol	0.7 mL
	Sterile distilled water	0.3 mL
	Simple syrup + Nipagin/nipasol	100 mL
Phosphates, oral solution (Joulie solution)[b]	Phosphoric acid 85%	5.45 g
	Disodium phosphate 12 H_2O (di)	18.72 g
	Sterile distilled water (qs)	100 mL
Cysteamine 0.55% eye drop solution[h]	Benzalkonium chloride	0.045 g
	Sodium chloride 0.9%	225 mL
	Cysteamine hydrochloride	1.2375 g

[a] Trissel LA. Trissel's Stability of Compounded Formulations. 3rd Ed. American Pharmacists Association, Washington DC; 2005:388–389.
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qs: quantum sufficiat (suffiecient quantity)

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