## WHAT IS CYSTINOSIS?

Cystinosis (OMIM 219800, 219900, 219750) is an autosomal recessive disorder with an estimated incidence of 1 case per 100,000 to 200,000 live births. The gene for cystinosis, CTNS, resides on chromosome 17p13 and encodes a lysosomal cystine transport protein called cystinosin.

Cystinosis results from defective cystinosin which is dysfunctional and causes impaired transport of cystine from the lysosome into the cytoplasm and interferes with other aspects of cellular function as well. The end result is excess lysosomal storage of cystine and cystine crystal formation in a wide variety of cells.

Recent experimental evidence has demonstrated that many aspects of cellular signaling are abnormal in cystinosis and may contribute to the clinical spectrum of the disorder in addition to crystal formation.

## CLINICAL CHARACTERISTICS

There are generally three presentations of patients with cystinosis: nephropathic cystinosis may occur during infancy and early childhood (the most common presentation) or have a later onset, often with a delay into young childhood or early adolescence (and has been called intermediate in the literature). Lastly, a disorder localized to cystine accumulation in the cornea is termed ocular cystinosis, and is relatively rare among the overall disease phenotype.

The initial manifestations of infantile nephropathic cystinosis, which accounts for ~ 95 percent of cases, generally appear several months after birth and include the following:

- A generalized renal Fanconi syndrome – leading to excessive polyuria, polydipsia, multiple electrolyte deficiencies, clinical dehydration (volume depletion), and generalized rickets
- Failure to thrive, including growth failure
- A reduction in glomerular filtration rate, leading to end-stage renal disease requiring dialysis or kidney transplantation in the first decade of life if not treated
- A later childhood onset of photophobia, resulting from crystal formation in the cornea

**Late-onset cystinosis**, or "juvenile" cystinosis, may have some of the same features as the nephropathic form, but may also exist without a generalized Fanconi syndrome, but with a markedly later age of onset and sometimes with a slower rate of progression into end-stage kidney disease. Additionally, the late-onset form of cystinosis may present as a primary nephrotic syndrome, which on biopsy appears as focal segmental glomerulosclerosis and may be confused with that entity.

**Ocular**, or non-nephropathic cystinosis, the rarest form of cystinosis, is characterized by the ocular findings typical of nephropathic cystinosis. However, other systemic manifestations are lacking: kidney disease does not occur.

## OUR MISSION

The Cystinosis Research Network is a volunteer, non-profit organization dedicated to supporting and advocating research, providing family assistance and educating the public and medical communities about cystinosis.

## OUR VISION

The Cystinosis Research Network's vision is the acceleration of the discovery of a cure, development of improved treatments and enhancement of quality of life for those with cystinosis.

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CYSTINOSIS RESEARCH NETWORK

302 Whytegate Ct, Lake Forest, IL 60045
Toll Free **1-866-276-3669**
Tel 847-735-0471 | Fax 847-235-2773
**info@cystinosis.org | www.cystinosis.org**


CYSTINOSIS RESEARCH NETWORK

Dedicated to a Cure. **Committed to Our Community.**

# CYSTINOSIS INFORMATION

## for Medical Professionals

## DIAGNOSIS

Three primary means are used to diagnosis cystinosis. They are:

1. Demonstration of elevated cystine content in a mixed white blood cell or in a granulocyte assay
2. Identification of crystals by slit-lamp examination of the corneas
3. Molecular testing of the CTNS gene

## TREATMENT

The earlier the diagnosis of cystinosis and institution of therapy is made, the more successful the outcome both for the kidney and for other clinical manifestations. The therapeutic needs of an affected patient depends on their particular manifestations at the time of diagnosis, and fall into two categories, supportive and specific therapies.

## SPECIFIC THERAPY WITH CYSTEAMINE BITARTRATE COMPOUNDS

Cysteamine is an aminothiol that results in depletion of lysosomal cystine; institution of such therapy early in life helps to retard renal functional deterioration of the kidneys, including as measured by the glomerular filtration rate (GFR) and also improves failure to thrive when used in combination with other supportive medications (see below). The two FDA and EMA approved preparations of cysteamine bitartrate are Cystagon®, absorbed in the stomach and given every 6 hours, and Procysbi®, which is given every 12 hours because of its intestinal delayed and prolonged release formulation.

**Cysteamine Dosage:** For Cystagon®, start at a daily dose of 10 mg of free base per kilogram of body weight per day, given in divided doses every 6 hours and increased weekly or biweekly by 10 mg per kilogram per day as the drug is tolerated, until a target dose of 60 to 90 mg per kilogram per day is reached; target leukocyte cystine content is less than 1.0 nmol of half-cystine per milligram of protein and < 1.9 nmol nmoles per milligram of protein/m2 for the granulocyte assay. The recommended starting dosage of Procysbi® for cysteamine-naïve patients is 0.2 to 0.3 grams/m2 per day divided into two doses given every 12 hours. A titration period of 4 to 6 weeks starting at 1/2 to 1/4 of the maintenance dose helps reduce the risk of side effects. Both preparations of cysteamine bitartrate max dose should not exceed 1.95g/m2/day

**Corneal Crystals:** These do not dissolve with oral cysteamine therapy, but do respond to the administration of cysteamine eyedrops. With frequent administration of eyedrops, ocular symptoms regress within weeks and the corneas clear within months to years. Cysteamine eyedrops have been approved by the FDA as Cystaran™.

## SUPPORTIVE THERAPIES

**Fanconi Syndrome:** The Fanconi syndrome in nepropathic cystinosis is one of the most difficult manifestations of the disease to treat, generally necessitating unrestricted intake of water and salt, supplementation with alkali solutions including sodium bicarbonate and/or citrate based therapies, calcium, sodium phosphate, the active vitamin D metabolite, 1,25-dihydrotachysterol, and sometimes L-carnitine.

**Failure to thrive/Growth failure:** Both adequate caloric intake, control of the biochemical Fanconi syndrome, and in some cases, the use of gastrostomy tubes to aid in nutrition and fluid intakes, and drug administration combined with cysteamine bitartrate to achieve desired target levels in the biomarker discussed above, are used to reverse the failure to thrive. In selected cases, recombinant human growth hormone may be needed as well.

**Skeletal deformities/Muscle weakness:** Evaluation by an orthopedic surgeon, timely and consistent physical and rehabilitation therapy with professional services help prevent and to improve multiple musculoskeletal issues. Surgery may be needed for bony deformity correction. Poor motor coordination and muscle weakness (myopathy) may occur in young adults and get progressively worse over time. Regular physical exercise should be an integral part of each patient's routine.

**Neurological:** Academic difficulties, cognitive deficits in visual spatial skills and visual memory, low muscle tone, fine motor incoordination. increased frequency of elevated intracranial pressure, seizures, memory problems, psychosocial issues and progressive cognitive dysfunction in adulthood may be present.

**Hypothyroidism:** Levothyroxlne therapy

**Hypogonadism:** Testosterone replacement (for adult males with low testosterone)

**End-stage renal disease:** There are several options including kidney transplantation, or peritoneal dialysis or hemodialysis. Kidney donors include living donors related or unrelated or being wait listed for a decreased donor kidney transplant.

The psychosocial and emotional impact of the disease on patients and families is significant. Ongoing involvement with social work and mental health services may be beneficial.