

CYSTINOSIS

TRANSITION MANAGEMENT TOOL



CYSTINOSIS
RESEARCH NETWORK

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Introduction

In the past, cystinosis, a rare genetic disease, had high childhood mortality. However, general advances in medical care and the development of an effective therapy for cystinosis has allowed many patients with this disease to have productive lives as adults. This has created the need for a user friendly concise tool with management guidelines since many primary and specialty care internal medicine practitioners are unfamiliar with cystinosis.

This tool was developed by pediatric and adult providers with experience in the care of patients with cystinosis to assist physicians less experienced in this rare disease to improve transition of care.



Cystinosis and the associated symptoms are life-long struggles. However, certain symptoms may present at a certain age or become increasingly challenging at key points in the human life-cycle.

Infancy and Childhood

- Genetics and Pathophysiology
- Nephrology
- Gastroenterology
- Ophthalmology
- Neurology
- Endocrinology
- Diet
- Speech therapy
- Physical Therapy/
Rehab Medicine

Adolescence

- Transplant
- Sexual maturation
- Neurology
- Pulmonology
- Psychosocial concerns
- Orthopedics

Adulthood

- Genetics
- Neurology
- Pulmonology
- Cardiology
- Sexual maturation
- Psychosocial concerns



Genetics and Pathophysiology

Cystinosis is an autosomal recessive disorder that occurs due to mutations in the CTNS gene, which codes for the transport protein cystinosin. Cystinosin transports the amino acid cystine out of lysosomes, but this does not occur in patients with cystinosis.

This leads to cystine accumulation in lysosomes, which causes cell dysfunction and injury. While renal manifestations dominate early in the disease, all organs are ultimately affected. Most patients with cystinosis have the severe nephropathic form, although there is a milder juvenile form and an ocular form without systemic manifestations. Diagnosis is usually made by measuring WBC cystine levels at cystinosis diagnostic laboratories.

Treatment with Cysteine-depleting Agents

The course of the disease was dramatically improved by the discovery that cysteamine effectively removes cystine from lysosomes. This therapy alters the course of cystinosis, including delaying the development of kidney failure and other systemic manifestations. Currently, cysteamine is available in an immediate-release form (Cystagon®) that requires dosing every six hours.

A delayed release form of cysteamine bitartrate (ProCysbi®) was recently approved and only requires dosing every 12 hours.

Cysteamine therapy is associated with side effects, including gastrointestinal symptoms and a sulfur odor. Dosing of cysteamine is adjusted based on measurement of WBC cystine levels.

Cysteamine therapy must continue after kidney transplantation since it is critical for ameliorating the widespread manifestations of cystinosis.

Nephrology

Cystinosis is the most common cause of Fanconi syndrome in children. Patients typically have dramatic wasting of electrolytes, and usually present with polyuria, polydipsia, episodes of dehydration, failure to thrive and rickets during infancy. Laboratory manifestations include metabolic acidosis, hypokalemia, hypophosphatemia (explaining the rickets), and glucosuria. Hypocalcemia and hyponatremia may also be present.



Therapy for the FS includes electrolyte supplementation and ready access to fluid. Many infants and children require gastric tube supplementation to provide medications, fluid and adequate nutrition. The losses of electrolytes decrease as kidney function declines, but even patients with advance kidney failure may have ongoing polyuria and require electrolyte supplementation. The FS does not recur post-transplant, but losses from the native kidneys may continue, and, in select cases, bilateral nephrectomies may be helpful.

Transplant

Transplant outcomes in this population are excellent. There are no known interactions of immunosuppressive medications with cysteamine, which may be restarted once a patient is able to eat and drink. Post-transplantation care is otherwise identical to other kidney recipients, other than the need to address systemic manifestations of cystinosis.

Sexual Maturation

Untreated patients nearly always exhibit late sexual maturation. Puberty starts at 15–17 years of age for male patients who are not treated or undertreated with cysteamine. Due to parenchymal tissue destruction and cystine accumulation within the testes, patients develop hypergonadotropic hypogonadism, low levels of testosterone and high levels of luteinizing hormone and follicle-stimulating hormone. Patients may benefit from testosterone supplements for secondary sexual characteristics. Infertility is common; no cystinosis patient is known to have fathered a child, but the ability to have an erection remains intact. Consideration should be given for sperm banking via testes or epididymis biopsy or the use of a donor sperm for infertile male adolescents and young adults.

In females with cystinosis who are untreated or undertreated with cysteamine, puberty is generally reached at 14–15 years of age. Ovulatory cycles and gonadal endocrine parameters are normal and successful pregnancies and deliveries have been observed. As is true of most rare autosomal recessive disorders, there is a very low risk of offspring from cystinosis patients having the disease.



Consider birth control options to avoid unplanned pregnancy. The pregnancies are at a higher risk for premature delivery and must be monitored closely. The teratogenicity of oral cysteamine in humans is not known; care must be taken to avoid exposing a fetus to cysteamine. It is a USFDA schedule "C" drug. For women who are post-transplantation, the abdominal renal allograft creates mechanical issues. Immunosuppressive regimen needs to be adjusted if pregnancy is planned. For women who have not undergone transplantation, fluid and electrolyte status require careful management.

Gastroenterology

Cystine crystal accumulation occurs in the upper and lower gastrointestinal (GI) tract. Cystinosis may be associated with intestinal dysmotility, causing symptoms such as vomiting, difficulty swallowing, abdominal bloating, and constipation. Cysteamine treatment may cause nausea, vomiting or abdominal pain. Patients may benefit from a gastroenterology consultation and those who have inadequate oral intake may require gastrostomy tube placement for supplemental feeding. Regular and effective cysteamine therapy may prevent or improve symptoms due to cystine accumulation. Acid suppression therapy will often reduce symptoms due to cysteamine. Those taking long-term regular acid suppressants should also receive calcium and vitamin D supplements.



Ophthalmology

Cystinosis results in the accumulation of cysteamine crystals in the cornea, causing light sensitivity, pain and blurred vision. This is usually diagnosed by slit-lamp examination. Crystal deposition can be halted, and accumulated crystals dissolved, by frequent use of cysteamine eye drops (Cystaran®). Effective therapy is often achieved by dosing 8-10 times daily. Patients require regular visits with a general ophthalmologist or cornea specialist, typically on a yearly basis. The doctor will also check for optic nerve swelling, an uncommon, but important finding that requires referral to neuro-ophthalmology or neurology for management.





Neurology

Many neurological problems can result from cystinosis, and they may appear at different ages. Poor motor coordination is often seen starting in young children, but continues throughout childhood and adolescence. Specific cognitive deficits in visual spatial skills and visual memory may cause difficulty in many areas of life, including academics. Academic difficulties may be present in school age children. Individuals with cystinosis may experience increased frequency of intracranial pressure (pseudotumor cerebri, benign intracranial hypertension), which requires prompt treatment to reduce pressure on the optic nerves and preserve vision. A congenital malformation of the brain, Chiari I malformation, is present at much higher rates in cystinosis patients. If a person with cystinosis develops new-onset headaches, double vision, balance problems or spasticity, or other unexplained neurological complaints, a brain MRI should be performed to look for a Chiari I. Treatment with surgical decompression of the cerebellar tonsils can alleviate symptoms. Seizures can occur at any age, but are more common in adults with cystinosis. Anti-epileptic medications may be required to control seizures.

Muscle weakness (myopathy) may occur in young adults and get progressively worse over time. There is a typical pattern of weakness that begins in the hands, moves to the shoulders, and then to the muscles of the mouth and pharynx, causing difficulty with phonation and swallowing. Diaphragm dysfunction can cause nocturnal oxygen desaturation. Treatment with cysteamine may delay the appearance or reduce the severity of the muscle weakness but may not have a definite effect on the myopathy or the other neurological symptoms. Adults with cystinosis may develop memory problems and progressive cognitive dysfunction. Psychosocial issues, including depression, may require intervention in adolescents and adults. A neurologist should be consulted if there are concerns about any of the above problems in a patient with cystinosis.



Cardiology

Cardiovascular problems in subjects with cystinosis may appear at different ages. Increased coronary calcification related to the accumulation of intracellular cystine has been observed in older subjects. High cholesterol levels might further add to the risk for

cardiovascular problems. In addition, chronic kidney disease may accelerate these cardiovascular changes and lead to congestive heart failure. There are rare reports of restrictive, noncompaction and dilated cardiomyopathies in patients with cystinosis. A cardiologist should be consulted if there are any concerns of cardiac involvement in cystinosis.

Endocrinology

Endocrine complications in cystinosis present at an early age, initially, as growth retardation and hypophosphatemic rickets with low serum phosphate. Secondary indications include high urinary losses of electrolytes and minerals, elevated levels of serum alkaline phosphatase, delayed ambulation, bone deformities, and osteomalacia. Patients require phosphate and vitamin D replacement and early initiation of growth hormone therapy to improve growth rate. Hypothyroidism usually develops in school age children. Screening blood testing is recommended on at least an annual basis. Elevated thyroid stimulating hormone and low free thyroxine are diagnostic features and L-thyroxine replacement is required. Delayed puberty and male infertility are common. Those who have low testosterone levels may benefit from testosterone supplementation since it may restore secondary sexual characteristics. Insulin dependent diabetes may develop in adult cystinosis patients. Exocrine pancreatic insufficiency may develop and pancreatic enzyme supplementation is necessary.



Pulmonology

Although the lungs are not directly affected by cystine accumulation, difficulty with breathing can still occur if cystine builds up and weakens the muscles that are used for ventilation, especially in older subjects. Pulmonary function tests can detect respiratory muscle weakness. It is recommended that such testing be done periodically for anyone who has weakness in other muscles of the body or for individuals who complain of inappropriate shortness of breath with exercise. For those with breathing problems, other conditions that can cause shortness of breath need to be excluded by obtaining a medical history, conducting a physical exam, and by performing some routine tests. Strategies to lessen the chance of developing breathing problems in people with cystinosis are to avoid cigarette smoking and to



keep up to date with immunizations to prevent lung infections, particularly influenza.

Respiratory muscle weakness is likely delayed or possibly prevented by cysteamine therapy. If respiratory muscle weakness becomes a major problem, patients with cystinosis can use various types of respiratory assist devices that deliver air under pressure via a face mask or nasal apparatus. This system can be used at night when sleeping or at other times during the day to rest the muscles that are used for breathing. As the muscles involved in swallowing become weaker, the risk of aspiration increases resulting in bronchitis or pneumonia. An early sign of aspiration is coughing that begins immediately at the time of eating. Experts in speech pathology can evaluate patients for swallowing problems and provide therapy to lessen the chance of oral contents entering the airway.

Diet

Energy requirements should be a minimum of DRI/age. The calorie requirements may be increased if a patient requires weight gain and could be as much as 1.5-2 times the DRI/age. If the patient has poor oral intake of solid food and is unable to meet calorie requirements, then a high calorie oral supplement or modular may be necessary. In some instances, a patient may not be able to meet calorie requirements on his/her own and may need placement of a gastric tube. In addition to meeting calorie requirements, a patient must also maintain adequate hydration and requires large amounts of water. Patients with cystinosis typically crave salty and/or spicy foods, secondary to the urinary losses. If medically appropriate, growth hormone may be recommended to improve patient's growth velocity.

Speech Therapy

Difficulties in feeding are common in cystinosis children. Refusal to eat is related to lack of hunger, secondary to intake of large amount of water, sensorimotor limitations in oral area, changed taste, perception disorder and behavioral refusal. Frequent vomiting and choking episodes are common. Food aspirations are usually due to insufficient reduction of food placed to mouth, inexperience and lack of coordination in the swallowing sequence.



Many children who are fed by gastric tube lose interest in chewing and swallowing. Therapy needs to be directed to train the muscles of mastication to stimulate oral ingestion of solid food and training of sensory perception through smells and flavors. Patients with feeding problems should be referred for evaluation by a swallowing team and speech therapist. Swallowing problems leading to choking episodes are increasingly seen in adults with cystinosis. Early evaluation with swallow study and early therapeutic intervention is of great importance in prevention of complications.

Physical Therapy/Rehab Medicine

Nephropathic cystinosis is a disorder involving muscular and skeletal functions requiring multiple musculoskeletal rehabilitation interventions.

Infants and toddlers with FS and delay of motor skills will benefit from physical therapy (PT); early referral is important. Rickets of FS requires evaluation by a rehabilitation medicine specialist and appropriate physical therapy prescription. Due to valgus or varus ricketic deformities, children will benefit from fitting of orthotics to modify body biomechanics and for proper skeletal alignment in order to prevent stress loads on the hip, knee and spine joints. Muscle hypotonia is an indication of PT and improved muscle tone. Combined approaches for correction of skeletal and muscular deficiencies is preferable. Post-surgery rehabilitation in patients after lower extremities corrective surgeries is necessary.

For adolescents and adults, intensive PT and combined orthopedic rehabilitation evaluation is necessary if skeletal deformities persist, to prevent osteopenia (to increase muscle load on the bones and to prevent and correct scoliosis. Fracture prevention education and rehabilitation of the patients with a history of fractures due to osteopenia/renal osteodystrophy is important. Targeted exercise prescriptions to the patients with upper extremities weakness (hands, forearms) by a PT specialist is recommended. Patients with chest muscle weakness require spirometry exercises to minimize restrictive lung disease and improve oxygenation. General exercise and activities prescription is indicated for all patients with myopathy/muscle wasting/ weakness. Patients with a history of rickets and renal osteodystrophy /osteomalacia will benefit from calcium, phosphate and vitamin D supplementations. Patients with



moderate to severe onset of myopathy and weakness might also benefit from a “mitochondrial cocktail” (Vitamins B6, C, CoQ10) and carnitine supplementations.

Psychosocial Concerns

Young adults transition from pediatric to adult-oriented healthcare at a time when they are also experiencing changes in legal status, education, work, insurance, and navigating adult relationships. Awareness of the patient’s rights under disability laws such as Individuals with Disabilities Education Act (IDEA) and the Americans with Disabilities Act (ADA) can help patients negotiate needed accommodations at college or work. Insurance coverage, including the extension of dependent coverage, should be discussed with patients and families, prior to transfer, so that access to healthcare and medications is not interrupted. Eligibility for Medicaid may change at age 18 and Medicare coverage for transplant patients is time-limited. Self-management of illness and adherence to treatment regimen is extremely important and extremely challenging in adolescence and young adulthood, necessitating open and honest communication, as well as skill-building. Mental health assessment, counseling, or social work consultation may be beneficial to manage the potential for depression or adjustment difficulties. A transition readiness checklist can assist teams and families in assessing young adult’s readiness to transition, numerous resources related to transition are available on the *GotTransition* website (<http://www.gottransition.org/family-information>).

Orthopedics

Orthopedic issues in cystinosis are common and result from the hypophosphatemic rickets and osteomalacia. Bone deformities are common, as is pain. Bone deformities can have a dramatic impact on the quality of life and ambulation in these children. Surgery is needed for correction of bone deformities. This may be in the form of growth modulation procedures (that use the child’s own growth to correct the deformity) for some of the less severe deformities, or osteotomies (cutting the bones) for realignment of the more severe deformities. Bracing may be useful for prevention of deformities or their recurrence in selected cases. Osteomalacia and myopathy may also contribute to musculoskeletal pain in



these children and need to be treated with appropriate metabolic control, vitamin D, and physical therapy. Early referral to an orthopedic surgeon familiar with this condition and monitoring may be beneficial as is treatment of deformities early with less invasive/simpler procedures (such as growth modulation).

Laboratory

Laboratory monitoring in adults with cystinosis should be designed to anticipate and correct complications of progressive organ dysfunction. Routine measures of glomerular filtration rate (eGFR), bone health, electrolytes, acidosis and other complication of renal dysfunction should reflect the CKD stage and severity of renal FS. In addition, regular lab testing should monitor status of the thyroid gland (T4, TSH), bone marrow (CBC), gonadal (testosterone, FSH and LH) and pancreatic endocrine (glucose tolerance test) and exocrine dysfunction (fat-soluble vitamins). Occasional testing for cholesterol and myocardial ischemia reflect the propensity for adult cystinotics to develop cardiovascular complications. Annual laboratory evaluations overseen by neurologists and occupational therapists are warranted to assess peripheral myopathy, swallowing disorders and brain dysfunction.

Common to all cystinosis patients is the need for ongoing monitoring of mixed leukocyte cystine level X 3-4/year. This encourages adherence with cysteamine therapy and guides dose adjustment with changes in body size or in accordance with clinical goals. This special test requires establishing a local arrangement for timed, point-of-care isolation of mixed leukocytes from "trough" blood drawn in the morning just prior to the next cysteamine dose (6-8 hrs after the last dose of Cystagon or 12 hours after the last dose of Procysbi). The leukocyte pellet is then transferred to a reference laboratory for assay. The therapeutic target (about 15-20% of untreated baseline) is $<1\text{nmol "half-cystine"/mg protein}$.



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