

CYSTINOSIS IN ADULTS:

Clinician Quick Reference



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CYSTINOSIS OVERVIEW

- Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *CTNS* gene and characterized by progressive cystine accumulation in lysosomes throughout the body^{1,2}
- Cystinosis has been classified into 3 forms: nephropathic (or infantile) cystinosis, intermediate (or juvenile) cystinosis, and non-nephropathic/ocular cystinosis. As nephropathic is the most common and severe form, this handbook will primarily focus on the care of these patients³

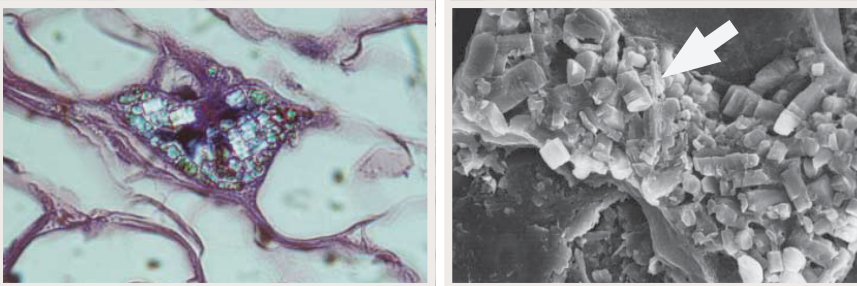
PATHOPHYSIOLOGY

Typically, the amino acid cystine—a product of protein degradation—is able to exit the lysosomal membrane through the transporter cystinosin, where it is reduced to 2 cysteine residues in the cytoplasm.^{1,3} As a result of defective or absent cystinosin in individuals with cystinosis, this transport process is impaired, resulting in continuous intralysosomal cystine accumulation and the eventual precipitation of cystine crystals.¹

In addition to cystine accumulation, several cellular processes are impacted by mutations in *CTNS*, including autophagy, apoptosis, and energy metabolism, which are now understood to contribute to the disease process.⁴

Cystinosin is expressed throughout the body, leading to multisystem dysfunction, with the kidneys being one of the organs most susceptible to damage.^{4,5}

Cystine crystal formation in a 37-year-old man with cystinosis⁶



Crystals seen with polarizing microscopy (left) and scanning electron microscopy (right).
Reproduced with permission from Singh K, Kusior MF. *N Engl J Med.* 1999.

NATURAL HISTORY

In early life, individuals with cystinosis experience renal tubular Fanconi syndrome, rickets, impaired growth, hypothyroidism, and photophobia.⁷ Eventually, these patients progress to end-stage renal disease and require renal replacement therapy and then renal transplant.⁷ After renal transplant, cystine continues to accumulate in nonrenal organs, shifting the burden of disease to other complications, including myopathy, endocrine dysfunction, and ophthalmologic progression.⁸

Historically, patients with nephropathic cystinosis were given a lifespan of ≈ 10 years.^{7,8} However, as a result of improved medical care, including renal transplant and early initiation of cystine-depleting therapy (CDT), individuals with cystinosis are living longer, with some living into their 50s.^{9,10}

PRIMARY CYSTINOSIS CARE

Treatment for cystinosis involves both (i) supportive therapies to address renal and extrarenal complications and (ii) specific treatment with cystine-depleting therapy (CDT).¹ Nephrologists often manage kidney-related concerns and CDT for the care of individuals with cystinosis.^{3,5} They may also help coordinate supportive care and involve additional specialists to manage extrarenal complications.⁵

CDT allows for depletion of intralysosomal cystine¹¹

- CDT breaks cystine into cysteine and cysteine–cysteamine mixed disulfide, which can exit the lysosome independently of the cystinosin transporter, decreasing the amount of cystine in cells by as much as 95%.^{1,12}
- CDT works to lower the levels of cystine and may help limit or possibly delay damage to the body.^{2,8,13}
- Oral CDT does not remove all cystine from the eyes, necessitating the use of topical cysteamine eye drops.^{10,14}
- WBC cystine testing is used to monitor treatment with CDT; the prescribed CDT dosage is generally adjusted based on WBC cystine levels rather than renal function.¹¹

WBC CYSTINE TESTING


Intracellular cystine level in WBCs (mixed leukocytes) or in selected WBC types (granulocytes) is the only clinically available biomarker for gauging cystine depletion and allows for CDT adjustments and medication adherence monitoring.^{11,15}

- ### FREQUENCY OF CYSTINE MONITORING
- At least 4 times per year when at WBC cystine target (children)³
 - At least 1 to 2 times per year when at WBC cystine target (adults)³
 - Evidence shows that monitoring WBC cystine levels may lead to better long-term outcomes¹⁵

WBC CYSTINE TESTING OPTIONS (different therapeutic targets)¹⁵⁻¹⁹

Due to the possibility of a falsely low reading with a mixed leukocytes sample, it is recommended to use the granulocytes test when possible.^{3,20}

Test	Granulocytes (polymorphonuclear leukocytes)	Mixed leukocytes
	UC San Diego	BAYLOR GENETICS
Target	<1.9 nmol ½ cystine/mg protein	<1.0 nmol ½ cystine/mg protein*

 Cystine level collection kits are available free of charge for both tests.¹⁷

*Corresponds to <1.9 nmol ½ cystine/mg protein target in granulocyte testing.¹⁶ WBC, white blood cell.

PRIMARY CYSTINOSIS CARE (cont'd)

Renal replacement therapy and, ultimately, transplant treat underlying kidney disease¹¹

- Renal replacement therapy or transplant has historically occurred by 10 years of age,²¹ although this occurs later when patients are adequately treated with CDT^{22,23}
- Renal transplant has excellent long-term outcomes in cystinosis, with 87% graft survival and 97% patient survival in a long-term cohort study of 30 patients with cystinosis between 1980 and 2013²⁴
- Successful transplant prolongs survival but does not correct the systemic defect, as cystine continues to accumulate in all organs **except** for the transplanted organ^{7,11}
- After renal transplant, the primary goals of therapy are to prevent rejection of the renal graft and to delay or limit damage to other organs⁹

NEPHROLOGY-FOCUSED EVALUATIONS

Routine renal function tests, including urinary electrolytes and protein excretion^{5,9}

Monitoring of immunosuppressive therapy¹¹

Kidney ultrasound to evaluate renal allograft⁷

CARE COORDINATION: Along with evaluating the patient's kidney function, the nephrologist may also help coordinate care and refer patients to the appropriate subspecialists to evaluate and monitor extrarenal complications.^{9,15}

NONRENAL CARE IN CYSTINOSIS

Despite renal transplant, cystine continues to build up in other organs throughout the body, and by adulthood, nearly every organ system is impacted.¹⁰

In addition to renal and WBC cystine monitoring, adults with cystinosis require evaluations to assess and manage nonrenal organ dysfunction.⁵

BODY SYSTEM



OPHTHALMOLOGIC PROGRESSION, with retinal and corneal cystine accumulation contributing to loss of visual acuity and worsening photophobia¹⁴

MANAGEMENT CONSIDERATIONS

- Oral cysteamine may allow for retinal depletion of cystine while topical cysteamine eye drops may help to delay or reduce corneal crystals. Both treatments are needed to preserve visual acuity^{a,10,14}
- There are currently 2 available options for topical cysteamine eye drops in cystinosis¹⁰

SUGGESTED MONITORING

ONCE PER YEAR:

- Eye examination, including slit-lamp biomicroscopy, intraocular pressure, and dilated fundus^{3,7,11}

EVERY 2 YEARS (or as indicated):

- Photopic and scotopic electroretinogram if patient reports altered night vision or has abnormal retinal examination findings¹¹



ENDOCRINE DYSFUNCTION, including hypothyroidism, diabetes mellitus, primary hypogonadism/azoospermia in males, hypoparathyroidism, and growth hormone deficiency^{2,8,25-28}

Patients may require the following:

- Levothyroxine for hypothyroidism^{7,11}
- Insulin for diabetes^{7,9,11}
- Testosterone for male hypogonadism^{7,11}
- Family planning/ preconception counseling for both men and women¹⁵
- Correction of vitamin D and PTH, and regular physical activity for bone health^{15,27}

EVERY 6 MONTHS (if stable):

- Thyroid panel (TSH and T4)²⁹
- Hemoglobin A1c²⁹

ONCE PER YEAR (if stable):

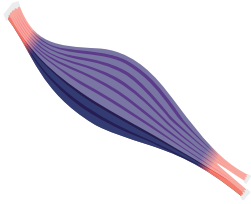
- Males: FSH, LH, testosterone, prolactin, inhibin B^{11,26,29}
- Females: FSH, LH, estradiol, anti-müllerian hormone, prolactin²⁷
- Bone health assessments (bone age, IGF-1, calcium, phosphorus, alkaline phosphatase, 25-hydroxy vitamin D, PTH, radiographs for bone deformities)^{11,27}

^aEvidence from a retrospective study of 29 patients with nephropathic cystinosis supports the potential that oral cysteamine may delay retinal infiltration of cystine.¹⁴

FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; PTH, parathyroid hormone; T4, thyroxine; TSH, thyroid-stimulating hormone.

NONRENAL CARE IN CYSTINOSIS (cont'd)

BODY SYSTEM



MYOPATHY, typically starting in the hands and progressing proximally to swallowing dysfunction and respiratory muscle weakness/restrictive lung disease^{30,31}

MANAGEMENT CONSIDERATIONS

- Myopathy may be present even before patient report/clinically recognizable weakness^{32,33}
- Encourage regular physical activity and/or physical therapy^{15,27}
- Patients with restrictive lung disease may require nighttime noninvasive ventilation⁹
- Electromyography may be irrelevant as atrophy after adolescence is usually a result of cystinosis-related myopathy⁷

SUGGESTED MONITORING

ONCE PER YEAR:

- Muscular examination (hand grip, MRC scale)^{3,11}
- Physical examination of orofacial motor function/swallowing¹¹
- Pulmonary function tests, spirometry, oxygen saturation, blood gas, and sleep study^{9,11}

EVERY 2 YEARS (or as indicated):

- Swallow study/modified barium videofluoroscopy^{7,9}
- Electromyography^{7,9}



GASTROINTESTINAL CONCERNS, most commonly presenting as nausea and vomiting³⁴

- GI concerns are nearly universal in patients with cystinosis³⁴
- 5-HT3 receptor antagonists may be helpful for nausea and vomiting⁹
- Esomeprazole or omeprazole can help with gastric acid hypersecretion^{9,35}

- Consider monitoring nutritional status for GI concerns and/or poor appetite⁷



VASCULAR CALCIFICATIONS, related to aging, diabetes, and time off CDT^{8,36}

- Current research suggests that cystine plays a role in calcification and that this complication is not a direct result of end-stage renal disease³⁶

ONCE PER YEAR:

- Lipid profile (total cholesterol, LDL, HDL, and TG)¹¹

EVERY 2 YEARS (or as indicated):

- Imaging studies to detect coronary or cerebral calcifications⁷

NONRENAL CARE IN CYSTINOSIS (cont'd)

BODY SYSTEM



CNS INVOLVEMENT, including intracranial hypertension, Chiari 1 malformation, and neurocognitive deficits with attention challenges and concerns for executive dysfunction and visual-spatial abilities³⁷⁻³⁹

MANAGEMENT CONSIDERATIONS

- Focus on organization/structure, using routines, promoting consistency, breaking down tasks, and employing organizational aids (eg, checklists) for patients with executive dysfunction³⁹
- Acetazolamide, furosemide, or ventriculoperitoneal shunt placement for intracranial hypertension^{7,9}

SUGGESTED MONITORING

ONCE PER YEAR:

- Neuropsychologic and psychosocial assessment^{3,11}

EVERY 2 YEARS (or as indicated):

- Brain MRI/CT scan with new-onset neurologic symptoms^{7,9,40}



Less common complications can also occur in adults with cystinosis, including liver enlargement, hypersplenism, hematologic complications (anemia, thrombocytopenia, or pancytopenia) unrelated to kidney failure, and cystine deposition in the skin associated with skin atrophy and premature aging.¹⁰



Cystinosis has a major impact on patients' physical health, autonomy, and ability to maintain relationships and may lead to **poor mental health, including anxiety and depression**.⁴¹ Additionally, patients who have survived past their projected lifespan may take on a fatalistic perspective, where they view themselves as having "no future to lose."⁴¹

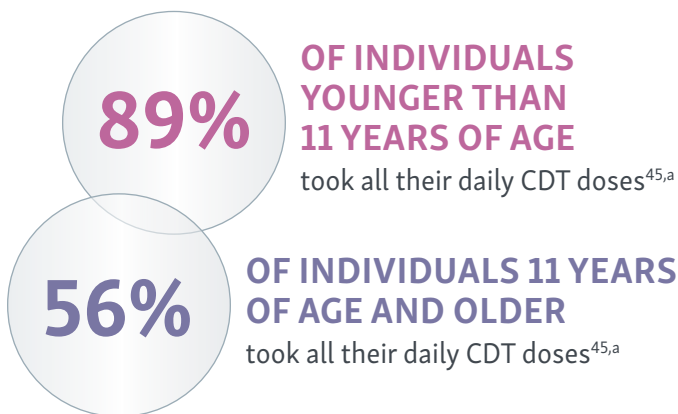
TREATMENT ADHERENCE

Individuals with cystinosis are living well into adulthood and are facing new challenges, including the need for lifelong adherence to multiple medications, such as immunosuppressive drugs, CDT, and other therapies.^{3,11} **Treatment adherence is a known barrier to effective management of chronic medical conditions and tends to decline in adolescence and adulthood, placing this group at risk for poor outcomes and graft loss.**^{11,15,42,43}

Risk factors for poor treatment adherence include^{11,43,44}:

- Dosing schedules
- Polypharmacy
- Duration of treatment
- Lack of perceived benefit
- Side effects
- Limited knowledge of the disease/medications
- Disease fatigue/denial
- Difficult transition to adult care

In a self-reported survey representing 61% of the cystinosis population in Spain, adherence tends to decline in adolescence and adulthood, placing these groups at risk for worse outcomes.^{15,45,46,a}



^aData from cysteamine adherence survey completed by patients (15/34) or their caregivers (19/34).⁴⁵



Research has shown that instilling and maintaining hope for the future

is an important motivator for maintaining patient engagement in care.⁴¹

SUPPORTING TREATMENT ADHERENCE^{11,44}

- Simplifying medications and developing individualized treatment plans
- Enlisting the help of a specific support person
- Identifying cues/visual reminders (eg, medication calendars, pill organizers, etc)
- Encouraging involvement in patient support organizations/programs
- Implementing and reinforcing disease education with the full care team
- Using questionnaires and laboratory studies (eg, drug assays, WBC cystine levels) to monitor adherence

SUPPORT FOR ADULTS WITH CYSTINOSIS

Many individuals with cystinosis find strength in the cystinosis community through mentorship opportunities, exchanging information, and cultivating connections with others.¹⁰

Resources for Patients

EDUCATION



COMMUNITY SUPPORT



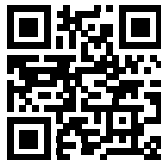
TRANSITION



Resources for Providers



Resources for clinicians who manage cystinosis
understandingcystinosis.com



Key open access publications from CRF
cystinosisresearch.org/published-studies



Information to share with patients on the impact of myopathy in cystinosis
cystinosisunited.com/cystinosis-signs-and-symptoms



Instructions for using WBC cystine level collection kits
wbckit.com



Quarterly *Cystinosis Circular* Newsletter

- Reach out to your Horizon contact to receive the next *Cystinosis Circular*



Information for clinicians who manage cystinosis
cystinosis.org/for-hcps

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