A SUPPLEMENT TO

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NEPHROPATHIC CYSTINOSIS: DIAGNOSIS, MANAGEMENT, AND CHALLENGES IN LONG-TERM TREATMENT

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Nephropathic cystinosis is a rare, inherited autosomal recessive disease caused by cystine accumulation in lysosomes.[1] A dysfunctional or missing cystine transport protein, cystinosin, causes accumulation of cystine, which is damaging to tissues and organs, especially the kidneys. Nephropathic cystinosis is an ultra-orphan disease with an incidence of about 0.5 to 1.0 per 100,000 live births.[1] There are an estimated 500 cases of nephropathic cystinosis in the United States and 2000 worldwide.[1,2] There are about 15 new cases in the United States each year.[1]

There are 3 main types of cystinosis based on symptom severity and age of onset (**Table 1**).[3] Infantile nephropathic cystinosis affects about 95% of patients and is usually diagnosed during the first 2 years of life. Juvenile nephropathic cystinosis is typically diagnosed in late childhood or during adolescence. Patients with juvenile nephropathic cystinosis have milder symptoms than those with the infantile type. The ocular form of the disease is diagnosed almost always during adulthood, with symptoms isolated to corneal cystine crystal deposits.

Table 1.
Three Main Types of Cystinosis[3]

Type	Characteristics
Infantile nephropathic cystinosis	• Diagnosed during the first 2 years of life • Most common (95% of cases of cystinosis) • Most severe
Juvenile or late-onset nephropathic cystinosis	• Diagnosed in late childhood or during adolescence • Milder symptoms than infantile type
Ocular or adult cystinosis	• Diagnosed in adulthood • Symptoms isolated to corneal cystine accumulation

MOLECULAR BASIS

All forms of nephropathic cystinosis are caused by mutations in the CTNS gene (17p13.2), which encodes the lysosomal cystine transporter cystinosin.[1,3] The CTNS gene is expressed in all cells.[4] The defective cystinosin transport process causes intralysosomal accumulation of cystine that crystalizes in most cells.[3,5] There are more than 100 reported mutations in the CTNS gene.[3] The most common mutation is a large 57kb base pair deletion involving exons 1 through 10. This founder mutation has been reported in greater than 60% of northern European patients with cystinosis.[1,3,6] Patients with infantile nephropathic cystinosis typically have 2 mutations that lead to complete loss of functional protein.[6] Milder mutations, associated with some residual protein function, occur in patients with the juvenile and ocular forms of the disease.[3]

NATURAL HISTORY

The remainder of this review focuses on infantile nephropathic cystinosis from childhood through adulthood. Cystine accumulation begins in utero, but clinical symptoms do not occur until the first months of life.[3,7] Renal tubular function is unaffected at birth, but symptoms of tubular dysfunction are present by 6 to 12 months of age.[5] Cystinosis is the most common cause of Fanconi syndrome in childhood. Fanconi syndrome, a generalized dysfunction of the renal proximal tubule, leads to

urinary wasting of water, electrolytes and other substances. Clinical manifestations include polyuria, polydipsia, failure to thrive, dehydration, vomiting, constipation, and rickets.[1,3,5] Laboratory testing is notable for metabolic acidosis, hypophosphatemia, hypokalemia, and hyponatremia. The urine usually has glucose and elevated levels of amino acids and low molecular weight proteins due to renal wasting. Patients untreated with cysteamine develop end-stage renal disease (ESRD) by 10 to 12 years of age.[3] Without cysteamine treatment, very few patients with infantile nephropathic cystinosis survive to the fourth decade, even with successful renal transplantation.[3]

While the kidney is the first affected organ, cystine accumulation damages organs throughout the body, with varying severity and timing. After the first year, corneal cystine crystal accumulation is visible by slit lamp examination.[3] Untreated, corneal cystine accumulation causes photophobia, typically during childhood.[1] Corneal crystals increase with age and, without treatment, result in blepharospasm, corneal erosions, and keratopathy.[3,7]

By 10 years of age, fibrosis, atrophy, and dysfunction of the thyroid gland develop in patients with nephropathic cystinosis.[1,3] Hepatomegaly and splenomegaly are found in about one-third of patients with the disease by 15 years of age.[3] Pancreatic dysfunction can lead to type 1 diabetes mellitus by late adolescence or early adulthood.[1,3] Left untreated, cystine accumulation causes a myopathy that is evident by young adulthood.[3] Symptoms include muscle weakness and atrophy, difficulty swallowing, and pulmonary dysfunction.[1,3]

Pubertal retardation can occur in both sexes, but is more severe in males. Hypergonadotropic hypogonadism develops in males and some boys require testosterone replacement therapy for proper pubertal development.[1,3] Gonadal dysfunction is milder in females, and several female patients with nephropathic cystinosis have gone on to have successful pregnancies.[3] Males are infertile.

Mild cognitive dysfunction has been reported in patients with nephropathic cystinosis, including visual motor, spatial, and memory skills—all of which may be caused by abnormalities in white matter. However, patients generally have normal overall intelligence.[1,3]

Juvenile nephropathic cystinosis manifests with much milder symptoms than the infantile type. Symptoms in the juvenile type usually emerge around age 10 years or older and the rate of disease progression is usually slower than seen in the infantile type.[7] In adult-onset cystinosis, only the eye is typically affected and photophobia is the most common symptom.[7]

DIAGNOSIS

Nephropathic cystinosis should be suspected in all patients who present with failure to thrive and symptoms of Fanconi syndrome (**Table 2**).[7] The typical patient with nephropathic cystinosis is an infant in the first year of life who presents with polyuria and resulting dehydration, failure to thrive, and vomiting. A basic chemistry profile will often reveal profound electrolyte abnormalities, including hypokalemia and hyponatremia. Suspected nephropathic cystinosis can be diagnosed by measuring leukocyte cystine levels, locating pathognomonic corneal cystine crystals using slit lamp examination, or analysis of the CTNS gene.[3] A white blood cell (WBC) cystine level >2 nmol ½ cystine/mg protein confirms the diagnosis; healthy subjects typically have WBC cystine levels <0.2 nmol ½ cystine/mg protein.[1] The standard treatment goal for patients with cystinosis is a trough WBC cystine levels <1 nmol ½ cystine/mg protein.[8] It is imperative that all suspected cases are diagnosed as early as possible and treatment begun promptly. Early initiation of cysteamine has a profound impact on long-term patient prognosis.[3]

Table 2.
Clinical Manifestations of Nephropathic Cystinosis[1,3,7]

Typical age of onset	Clinical finding
Infants/young children	• Fanconi syndrome o Polyuria o Polydipsia o Dehydration o Rickets o Metabolic acidosis o Hypokalemia o Hypophosphatemia o Hyponatremia • Failure to thrive • Hypothyroidism • Photophobia
Adolescents	• Myopathy • Hepatomegaly • Splenomegaly
Adults	• Pancreatic dysfunction o Diabetes mellitus • Hypogonadism (males) • Pulmonary dysfunction • Mild neurocognitive abnormalities • Central nervous system calcifications and symptomatic deterioration

MANAGEMENT AND TREATMENT

Fanconi Syndrome

Most patients with nephropathic cystinosis will present with

Fanconi syndrome and these symptoms should be addressed first. Children with Fanconi syndrome should have unrestricted access to water and salt to replace renal losses, which can be quite extreme.[1,7] Extended sun and heat exposure should be avoided because of the risk of dehydration and heat stroke (due to impaired sweating).[7]

Indomethacin has been used with some success to decrease polyuria, but should be stopped if patients are dehydrated, hypotensive, or if renal function deteriorates.[3] Electrolyte replacement therapy is necessary, and typically includes phosphorus, base (bicarbonate or citrate), potassium, and sodium.[1]

Nasogastric tubes or gastrostomy tube feeding is common in patients with nephropathic cystinosis, especially in young children. Improved fluid administration is particularly beneficial for children with feeding difficulties and during infections, when fluid imbalance can be more difficult to control.[1,3,9] Gastric tubes can also aid in the administration of oral medications.[3] Gastric tubes should be considered early to prevent dehydration and to facilitate fluid replenishment and electrolyte supplementation.

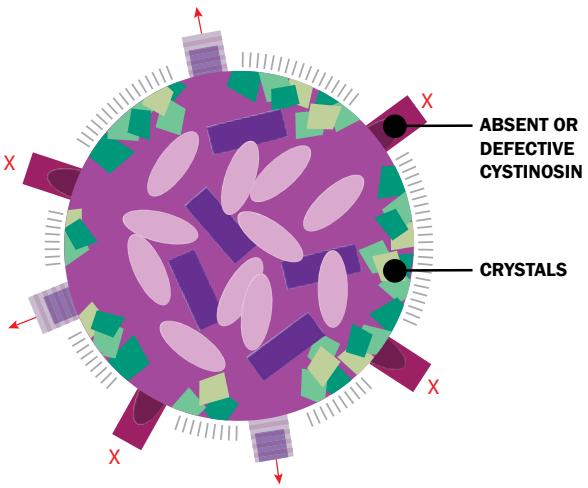
Cysteamine

Cysteamine was introduced as a treatment option for cystinosis in 1976 and remains the gold standard of therapy. Cysteamine gains entry into the lysosome through an unknown transporter and reacts with cystine to form cysteine and cysteine-cysteamine disulfide.[1,10] Cysteine and the cysteine-cysteamine disulfide leave the lysosome through a cysteine transporter and a second undefined transporter, thereby depleting cystine levels in cells (**Figure 1**).

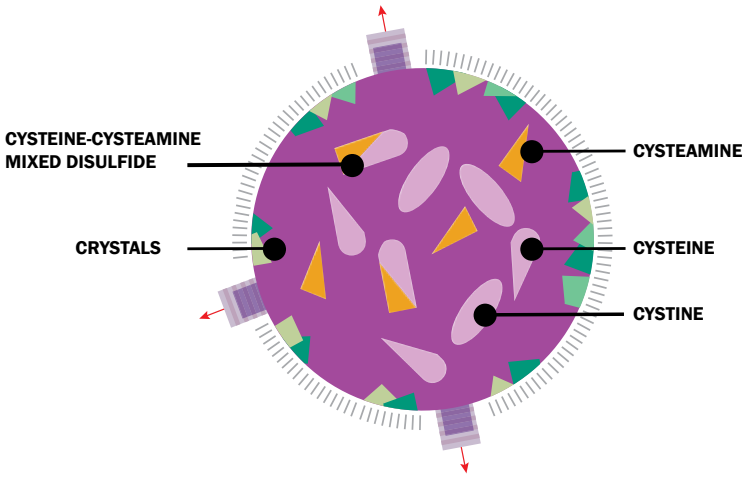
While not a cure for cystinosis, cysteamine dramatically improves a patient's prognosis—very few patients without cysteamine treatment survive beyond 30 years of age, even with successful renal transplantation.[3] Cysteamine therapy should be initiated immediately after diagnosis; this is especially important during the first year of life. Early administration of cysteamine can preserve the usual increase in renal function

Figure 1. Cysteamine Reduces Toxic Levels of Cystine[7]

A. Lysosome of patient with cystinosis



B. Cysteamine converts cystine into cysteine and a cysteine-cysteamine mixed disulfide that leave the cell via a cysteine transporter and second undefined transporter



that occurs during infancy, ultimately delaying transplant.[11,12] Ongoing treatment is critical for slowing deterioration of renal function. Other complications of the disease, such as hypothyroidism, diabetes, and neuromuscular disorders, occur less commonly or can be delayed or lessened in severity with early initiation of cysteamine treatment.[12]

Cysteamine is a life-long therapy, even after renal transplantation, as cystine accumulation continues in other organs and tissues. Fortunately, the renal allograft is not affected by cystinosis. Time off of cysteamine therapy is correlated with increased frequency of diabetes, myopathy, pulmonary dysfunction, and death.[5]

Cysteamine should be introduced at a low dose, with gradual increases over 4 to 10 weeks.[13] When the drug was first introduced, some patients developed hyperthermia, lethargy, and rash. These adverse effects were largely alleviated via a gradual increase in dose. The most commonly reported adverse effects of cysteamine treatment are gastrointestinal discomfort and unpleasant body odor or breath.

Gastrointestinal symptoms include nausea, vomiting, retching, abdominal pain, swallowing dysfunction, heartburn, and anorexia.[14] Many of these symptoms are acid-mediated and concomitant treatment with proton-pump inhibitors (PPIs) can provide relief.[14] Bad breath and body odor are caused by the sulfur compounds, dimethylsufide and methanethiol, both metabolites of cysteamine.[7,10] There is no standard treatment for the malodor associated with cysteamine, but some patients choose to take vitamin B2 supplements or use masking agents such as chlorophyll pills, essential oils, chewing gum, and mouthwash.[3,8] The benefits of these strategies have not been proven and are largely subjective.

Cysteamine should be taken in a fasted state. A study showed that cysteamine taken with high-fat/calorie or high-protein diets resulted in less consistent and decreased absorption. Food may affect the passage of cysteamine into the small intestine where it is optimally absorbed.[15] To achieve maximum cysteamine bioavailability, patients should avoid eating for at least 2 hours prior and 30 minutes after cysteamine administration. If fasting during these times is not possible, patients should limit their food intake to ~4 ounces or ~half cup of food and preferably carbohydrates, because absorption is especially diminished with high fat/high-protein meals. Patients should try to relieve gastrointestinal symptoms via other means, such as an acid-reducing agent.[15]

Immediate-Release Cysteamine

Immediate-release cysteamine bitartrate (IR-C) was approved by the US Food and Drug Administration (FDA) in 1994 for the treatment of cystinosis. This formulation of the drug, in capsule form, has a cystine-depleting effect that lasts 6 hours, requiring dosing every 6 hours around the clock.[8,9]

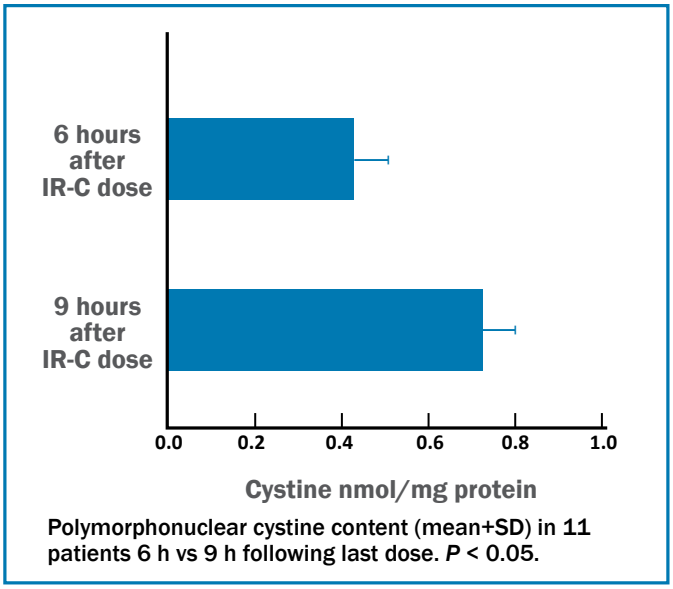
Adherence is a challenge with IR-C because of the rigorous dosing schedule, GI adverse effects, and sulfur odor.[8,11] A study showed that only 5 of 22 patients (23%) taking IR-C fully adhered to the 6-hour dosing schedule.[8] Another study reported that only 28% of patients had optimal leukocyte cystine levels, indicating nonadherence in over two-thirds of the study population.[12]

Patient age can also heavily impact treatment adherence. Infants and young children are more likely to have good adherence because they rely heavily on parents for scheduling and treatment. However, adherence is much more challenging in teenagers who are transitioning to more self-control of their own treatment.[2,8,16]

The benefits of strict cysteamine adherence are well documented.[11] Patients with consistent adherence can achieve up to 95% leukocyte cystine depletion and maintain low polymorphonuclear cystine levels.[8,12] Strict adherence can result in greater preservation of renal glomerular function and significantly delay ESRD.[12,17] Even a 2 to 3 hour delay in treatment can cause considerable cystine accumulation.[8] As shown in **Figure 2**, WBC cystine levels are significantly higher in patients who are tested 9 hours after IR-C administration compared with those tested after 6 hours.[8] Optimal treatment goal is a WBC cystine level <1 nmol ½ cystine/mg protein. Nonadherence can result in WBC cystine levels well above that objective.

Figure 2.

Interruption of Cysteamine Dosing Quickly Compromises Cystine Control[8]



Polymorphonuclear cystine content (mean+SD) in 11 patients 6 h vs 9 h following last dose. $P < 0.05$.

Delayed-Release Cysteamine

In a 2006 study, cysteamine administered directly into the small intestine demonstrated higher serum levels compared with administration into the stomach or colon. This suggested that a delayed-release formulation absorbed through the small intestine, rather than the stomach, was a potential therapeutic option for patients with nephropathic cystinosis.[18]

The delayed-release formulation of cysteamine bitartrate (DR-C) was approved by the FDA in 2013 for patients aged 6 years and older, and the label was expanded in 2015 to include children as young as 2 years. These micro-spheres allow every 12 hour dosing of cysteamine.

DR-C given at a dose approximately 60% to 70% of IR-C is effective in maintaining cystine levels in satisfactory range.[19,20] Non-inferiority to IR-C for control WBC cystine levels was shown in a randomized controlled crossover trial.[21] In the same trial, patients in the DR-C arm showed an 87% reduction in PPI use.[21] The patients receiving DR-C had a significant improvement in quality of life.[22] Twice-daily dosing is likely to be preferred by patients and, more importantly, it can have a significant impact on treatment adherence and quality of life. Guidelines for using IR-C and DR-C are summarized in **Figure 3.**

Cysteamine Ophthalmic Solution

Systemic cysteamine therapy does not effectively treat corneal cystine crystal accumulation, so concomitant therapy with cysteamine topical eye solution is nearly always required for these patients.[1,3] Cysteamine eye drops are highly effective and one drop should be administered in each eye every waking hour; however, actual adherence is more likely between 6 and 12 times per day.[3,7,25] Cysteamine eye drops dissolve corneal crystals completely within months and therapy should continue for life to prevent crystal accumulation.[1,7]

Growth Hormone

Growth retardation is a common symptom of nephropathic cystinosis. Historically, most patients who did not receive treatment with cysteamine were unable to attain full adult height.[3] Treatment with recombinant growth hormone should be considered if other symptomatic therapies are unable to avert growth retardation.[3] In patients with established growth retardation, growth hormone treatment allows patients to "catch up" and achieve normal height.[1,7]

Renal Transplantation

End-stage renal disease usually develops by age 10 to 12 years in patients who never receive cysteamine therapy.[3] Treatment with cysteamine delays renal transplantation, but does not ultimately prevent it.[13] Patients who are diagnosed early in life and initiate prompt treatment with cysteamine and remain adherent should prolong kidney life until late adolescence or early adulthood.[2,12,16] Dialysis is utilized until a donor organ is available.[1]

Patients with cystinosis have good outcomes with renal transplantation and have better five-year graft survival than patients with kidney failure from other etiologies.[3,16] The new kidney is unaffected by cystinosis; however, continued cysteamine therapy is necessary to prevent the myriad extra-renal manifestations of the disease. Cysteamine therapy should be resumed as quickly as possible post-transplantation.

Gene Therapy

The CTNS gene is expressed in every cell and tissue, making genetic therapy a challenging therapeutic option. Thus far, gene rescue has been tested in mouse models using autologous transplantation of hematopoietic stem cells (HSCs) ex vivo. Transplantation of HSCs with a functioning CTNS gene has shown some therapeutic benefit in mice, but clinical trials in humans are needed.[4]

TRANSITION OF CARE FROM PEDIATRIC TO ADULT NEPHROLOGISTS

Nephropathic cystinosis, once thought of as a fatal childhood disease, is now largely considered a chronic disease and patients in developed countries can survive into their 40s and beyond.[2] With the availability of cysteamine treatment, end-stage renal disease has been pushed from mid-childhood to late-adolescence and early adulthood.

Like most rare diseases that begin in childhood, adult providers may not be well informed about the condition or prepared for the long-term management of a small patient population. Adult nephrologists who are inexperienced with nephropathic cystinosis should be educated on the challenges associated with this disease. These include lifelong systemic cysteamine treatment, even after renal transplant; the long-term consequences of cystinosis; and the importance of treatment adherence and its associated challenges.[2]

Now that patients are living longer, a challenge has emerged within the cystinosis community regarding the transition of patients from pediatric to adult care. Pediatric nephrologists typically care for patients with the disease for many years and often develop a strong bond and sense of trust with these children and their families. Transition of care from a pediatric to an adult provider can be a difficult time for patients, especially if they feel the new provider is not knowledgeable about their condition. This transitioning phase is an opportunity for the pediatric nephrologist to develop clinical and referral relationships with adult nephrologists to help bridge the gap. Established partnerships between pediatric and adult providers will not only improve the flow of patient history, but will also offer much needed assurance to patients and families.[2] A mul-

Figure 3.
Practical Guide to Using Cysteamine[23,24]

	Immediate-release cysteamine (IR-C)	Delayed-release cysteamine bitartrate (DR-C)
Formulation	• Available in 50 mg and 150 mg capsules.	• Available in 25 mg and 75 mg capsules. • Most patients can be managed with either 25 or 75 mg capsules exclusively to avoid the need to prescribe two formulations (the 25 mg capsules are typically only needed when initiating/titrating therapy in patients <10-15 kg).
Dosing	• Every 6 hours. • The initial targeted dose should be 60 mg/kg/day (maximum initial dose: 2000 mg/day). The initial prescription may be made out for this dose to minimize paperwork, but patients should be instructed to follow the following dosage titration: o Initial dose: 15 mg/kg/day (maximum of 600 mg/day). o Increase dose over 4-6 weeks to 60 mg/kg/day. o Measure WBC cystine level when the patient reaches a dose of 60 mg/kg/day and has been on this dose for at least 1 week. o Titrate dose to obtain a therapeutic level. o The maximum dose is 90 mg/kg/day (1.95 g/m^2/day).	**Initiation in a patient who is not currently receiving IR-C** • The targeted dose should be for ~40-50 mg/kg/day (maximum initial dose: 2400 mg/day). The initial prescription may be made out for this dose to minimize paperwork, but patients should be instructed to follow the following dosage titration: o Initial dose: 10 mg/kg/day (maximum of 600 mg/day). o Increase dose every 1-2 weeks by no more than 10 mg/kg/day. o Measure WBC cystine level when the patient reaches a dose of 35-45 mg/kg/day and has been on this dose for at least 1 week. o Titrate dose to obtain a therapeutic level. **Conversion from IR-C to DR-C** • Initiate DR-C at 70% of the current daily cysteamine dose.[a] The current daily cysteamine dose should be the actual dose the patient is taking (eg, patient is prescribed 600 mg qid, but taking 600 bid, then start with 70% 0f 1200 mg, not 70% of 2400 mg). • Measure WBC cystine level in approximately 2-6 weeks. • Titrate dose to obtain a therapeutic level.
Dose adjustments	• Increase dose when WBC cystine level is above target. • Decrease dose for side effects. • Dose adjustments are generally ~10 mg/kg/day (maximum of 600 mg/day), rounding based on pill size (eg, change by 4 or 8 pills per day).	• Increase dose when WBC cystine levels are elevated. • Decrease dose for side effects. • Dose adjustments are generally ~5-10 mg/kg/day (maximum of 600 mg/day), rounding based on pill size (eg, change by 2 or 4 pills per day).
Administration	• The capsules can be opened and the contents placed in a liquid, but the entire dose should be taken within 5 minutes (ie, the liquid should not be slowly ingested over >5 minutes).	• Pills can be taken with water or juice. • The capsules can be opened and the microbeads placed in a liquid (apple juice or orange juice) or a soft food (apple sauce or berry jelly), but should not be chewed. They should be taken within 30 minutes. • The microbeads can be injected into a 14 French or larger g-tube (after mixing with apple sauce); a straight tube is preferred. The tube should be flushed with 2-8 ounces of orange juice or apple juice. • Ideally, should be taken fasted (no food 1 hour before or after). A small amount of food (4 ounces) may be taken if necessary, but avoid high fat foods. Good foods to take include applesauce, citrus fruits, or apples. Attempt to take in a consistent manner each day relative to the type and amount of food within 1 hour. It is more important to avoid taking with food than to take the pills exactly on a 12 hour schedule. If the patient is an adult or on dialysis, gastric emptying may be delayed, so waiting up to 2 hours after a meal may be necessary. • It can be taken with other medications (eg, Bicitra, Polycitra, vitamin D, phosphorus and potassium supplements) except for sodium bicarbonate.
WBC cystine measurement	• Reliable measurement of WBC cystine level is the current gold standard for monitoring. • Timing: obtain a trough level 5-6 hours after the last dose, but before the next dose. • Frequency of Monitoring: 1-2 weeks after reaches target dose and then every 1-2 months until reaches target level; then quarterly until stable (may then measure every 3-6 months).	• Reliable measurement of WBC cystine level is the current gold standard for monitoring. • Timing: obtain a trough level 12 hours after the last dose, but before the next dose. • Frequency of Monitoring o Initiation of DR-C (no current DR-C): 1-2 weeks after reaches target dose and then every 1-2 months until reaches target level; then quarterly until stable (may then measure every 3-6 months). o Conversion to DR-C from IR-C: 2 weeks after conversion and then quarterly until stable (may then measure every 3-6 months).

Abbreviations: bid, 2 times per day; qid, 4 times per day.
[a]The US Food and Drug Administration approved labeling for DR-C recommends initiating DR-C at 100% of the current IR-C dose.

tidisciplinary approach—including nephrology, ophthalmology, and other disciplines—is the optimal long-term solution for patients with nephropathic cystinosis.[9]

For individuals with nephropathic cystinosis the time of transition from pediatric to adult care overlaps with patient desire for greater autonomy in disease management and new education, work, and insurance situations.[2] Patients are expected to take a larger role in self-care as they transition to adulthood, but the transferring of disease management from parent to child can be met with reluctance and anxiety from both parties. It is, however, a necessary and developmentally appropriate transition.[2]

Providers and families should encourage a patient's emerging sense of independence and responsibility, while also providing counsel on the necessity of strict medication adherence and disease management. Patients should also be advised to develop self-care and self-advocacy skills as he or she transitions to an adult provider. Patients should be well informed about their disease and treatment history and have the ability to clearly communicate that information with adult providers. Patients should also be aware of advocacy groups that focus on cystinosis, such as the Cystinosis Research Foundation and Cystinosis Research Network, which can provide additional support and education for families affected by the disease.

CONCLUSION

Nephropathic cystinosis is a rare lysosomal storage disorder that causes accumulation of cystine crystals in all cells and usually develops in childhood. Historically, end-stage renal disease developed by 10 years of age, but with the introduction of the cystine-depleting agent cysteamine patients can delay kidney failure by as many as 10 to 15 years. Treatment adherence to cysteamine therapy is essential, but has presented a challenge because of rigorous dosing schedules — every 6 hours, around the clock — and unpleasant adverse effects. A new formulation of cysteamine offers a 12-hour dosing schedule and potential lessening of GI adverse effects. Treatment adherence is more likely with a 12-hour dosing schedule as it will not interrupt sleep, and patients can expect better quality of life.

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