Pediatric Nephrology
Journal of the International Pediatric Nephrology Association

10.1007/s00467-004-1777-5

Consensus Statement

First NIH/Office of Rare Diseases Conference on Cystinosis: past, present, and future

Robert Kleta[1], Frederick Kaskel[2], Ranjan Dohil[3], Paul Goodyer[4], Lisa M. Guay-Woodford[5], Erik Harms[6], Julie R. Ingelfinger[7], Vera H. Koch[8], Craig B. Langman[9], Mary B. Leonard[10], Roslyn B. Mannon[11], Minnie Sarwal[12], Jerry A. Schneider[13], Flemming Skovby[14], Barbara C. Sonies[15], Jess G. Thoene[16], Doris A. Trauner[17] and William A. Gahl[18, 19]

(1) Office of Rare Diseases, National Institutes of Health, Bethesda, Maryland, USA

(2) Children's Hospital at Montefiore, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, USA

(3) Division of Pediatric Gastroenterology and Hepatology, University of California, San Diego, California, USA

(4) Department of Pediatrics, McGill University Medical Center, Montreal, Quebec, Canada

(5) Division of Genetic and Translational Medicine, University of Alabama, Birmingham, Alabama, USA

(6) University Children's Hospital, Muenster, Germany

(7) Harvard Medical School, Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, Massachusetts, USA

(8) Pediatric Nephrology Unit, Instituto da Criança, Hospital das Clinicas of the Sao Paulo Medical School, Sao Paulo, Brazil

(9) Children's Memorial Medical Center, Chicago, Illinois, USA

(10) Division of Nephrology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

(11) Transplantation Branch, NIDDK, Bethesda, Maryland, USA

(12) Department of Pediatrics, Stanford University, Stanford, California, USA

(13) University of California, San Diego, La Jolla, California, USA

(14) Department of Clinical Genetics, University Hospital of Copenhagen, Copenhagen,

Denmark

(15) Ultrasound Imaging Laboratory, Department of Rehabilitation Medicine, National Institutes of Health, Bethesda, Maryland, USA

(16) Hayward Genetics Center, Tulane University School of Medicine, New Orleans, Louisiana, USA

(17) Department of Neurosciences, University of California, San Diego, California, USA

(18) National Human Genome Research Institute, Medical Genetics Branch, National Institutes of Health, 10 Center Drive, MSC 1851, Building 10, Room 10C103, Bethesda, MD 20892-1851, USA

(19) Section on Human Biochemical Genetics, National Institutes of Health, Bethesda, Maryland, USA

William A. Gahl
Email: bgahl@helix.nih.gov
Phone: +1-301-4022739
Fax: +1-301-4022740

Received: 8 October 2004 **Accepted:** 27 October 2004 **Published online:** 27 January 2005

Without Abstract

Keywords Cystinosis

Researchers and clinicians with expertise in cystinosis and related fields met on 12–13 May 2004 on the NIH campus for a 1.5-day symposium sponsored by the NIH Office of Rare Diseases, the NHGRI, and NIDDK, and supported in part by the Cystinosis Foundation and the Cystinosis Research Network. The meeting addressed the past, present, and future of nephropathic cystinosis research.

As background, nephropathic cystinosis is an autosomal recessive lysosomal storage disorder with an estimated incidence of 1 in 100–200,000 live births [*1*, *2*]. Patients appear normal at birth but generally develop failure to thrive and manifest renal tubular Fanconi syndrome, with its concomitant metabolic (normal anion gap) acidosis and volume depletion, electrolyte imbalances, growth retardation, and hypophosphatemic rickets by 6–12 month of age. Later, photophobia reflects progressive corneal crystal accumulation. In the natural history of untreated cystinosis, kidney failure occurs at approximately 10 years of age, requiring dialysis or kidney transplantation. Later in the untreated patient, extra-renal complications occur with varying frequencies. These include distal vacuolar myopathy, swallowing abnormalities, retinal blindness, diabetes

mellitus, pancreatic exocrine insufficiency, decreased pulmonary function, and neurological deterioration. More information on cystinosis and its molecular diagnosis can be obtained at http://www.genetests.org.

There was agreement on the importance of several topics related to the disease:

1. Early diagnosis is critical and relies upon the findings of failure to thrive and renal tubular Fanconi syndrome. Cystinosis remains the most common, and the most treatable, identifiable cause of renal Fanconi syndrome in children. Definitive diagnosis is accomplished by finding of an elevated leukocyte cystine level, generally 3–20 nmol half-cystine/mg protein, at any age. However, normal values are <0.2 nmol half-cystine/mg protein, and higher values should raise suspicion sufficient to warrant discussion of the case with an expert in cystinosis. This leukocyte cystine assay is available in the CLIA-certified laboratories of Dr. Jerry Schneider at the University of California, San Diego, and Dr. Jess Thoene at Tulane University School of Medicine. In addition to elevated leukocyte cystine levels, the finding of corneal crystals on slit lamp examination by an experienced ophthalmologist can also make the diagnosis, but some patients do not have crystals until 1–2 years of age. A reasonable goal would be to diagnose infants with cysinosis prior to 1 year of age. This aim can be accomplished if pediatricians, family practitioners, and pediatric nephrologists first consider cystinosis when they see signs and symptoms of renal tubular Fanconi syndrome. In addition, consideration should be given to developing a newborn screening test for cystinosis.

2. Treatment should employ a team approach, including a pediatric nephrologist, a metabolic disease expert, a genetic counselor, and a local pediatrician or family practitioner. Therapy involves ready access to water and salt, oral repletion with potassium and alkalinizing agents (e.g., citrate or bicarbonate), and provision of supplemental phosphate salts. In some cases, a vitamin D preparation is needed to increase intestinal absorption and decrease urinary losses of phosphate. Blood chemistry should be monitored frequently at the initiation of therapy, perhaps every other week for the 1st month and then monthly for 6 months. Stabilization of blood chemistry should be complete within several weeks and healing of rickets within 3–6 months. Oral cysteamine (Cystagon) therapy should be initiated within days of diagnosis. Ophthalmic examinations should be performed approximately every year to rule out idiopathic intracranial hypertension by finding flat optic discs. Neurological progress should be monitored on a regular basis to assess the presence of co-ordination problems and learning difficulties in childhood, and for myopathic changes and cognitive deterioration in adults. Linear growth should be evaluated approximately 6 months after optimal control of blood chemistry and initiation of Cystagon. If the growth velocity has not improved, or the patient remains below the 3rd percentile for height after a year of therapy, recombinant human growth hormone therapy should be considered

Renal transplantation is the treatment of choice for end-stage renal disease in cystinosis, and is completely curative for the Fanconi syndrome. Pre-emptive transplantation is preferred. Steroid minimization or avoidance after transplantation can help maximize growth potential. The use of carnitine for improvement in muscle function remains controversial, but may be used in selected circumstances.

3. Oral cysteamine therapy provides the mainstay of cystinosis treatment and should be started as soon as possible to prevent glomerular deterioration and allow for growth of renal function. Initial dosing is incremental (over approximately 2–4 weeks) to achieve 60 mg/kg per day given every 6 h, not q.i.d. Further dose increases, to between 60 and 90 mg/kg per day (or between 1.3 and 1.95 g/m^2 per day), should be implemented to achieve a leukocyte cystine level <1.0 nmol half-cystine/mg protein. Since <0.2 nmol half-cystine/mg protein is normal, consideration should be given to administering doses that achieve leukocyte cystine values approaching this level. (For example, doses >60 mg/kg per day can be prescribed to lower the leukocyte cystine value from 0.9 to 0.3 nmol half-cystine/mg protein.) The dose should never exceed 90 mg/kg per day of cysteamine free base. The dose recommended for adults is 500 mg every 6 h, but higher doses are often required to achieve satisfactory cystine depletion. Cystagon can be given with food or drink, but should be taken in bolus form (i.e., within 5 min) rather than dissolved and sipped over time. For patients with gastric acid-related symptoms, proton pump inhibitors may prove helpful. Cystagon, available in capsules of 50 mg and 150 mg of free base, is approved by the United States Food and Drug Administration to prevent renal function deterioration and enhance linear growth in pre-transplant cystinosis patients. However, based upon its salutary effects in maintaining thyroid function and depleting muscle of cystine, it should also be used in post-kidney transplant patients to help preserve other organs.

4. Transitioning of care from pediatric to adult services remains an important area of concern. Internal medicine-trained nephrologists, in particular, must become familiar with cystinosis in the adult patient. Pediatric nephrologists should assist their colleagues in this pursuit, specifically via interactions with societies of adult nephrologists. The establishment of centers for the care of cystinosis patients by both pediatric and adult specialists should be considered.

5. Future studies should include investigations into the value of therapies to reduce proteinuria, the possibility of newborn screening for cystinosis, and the development of alternatives to cysteamine for achieving cystine depletion.

The authors approve of these basic therapeutic tenets and are available to answer questions and discuss individual cases.

References

1. Gahl WA, Thoene J, Schneider JA (2001) Cystinosis: a disorder of lysosomal membrane transport. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The metabolic and molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, pp 5085–5108

2. Gahl WA, Thoene JG, Schneider JA (2002) Cystinosis. N Engl J Med 347:111–121