Global Action. Local Change.

KDIGO Controversies Conference on Nephropathic Cystinosis

Breakout Questions

1. Basic and translational science

1. How does cystine exit from cystinotic lysosomes to interact with cell metabolism, and how are the pathological effects of lysosomal cystine storage mediated?

2. Apoptosis is increased in cystinotic tissue and the increase is linked to lysosomal cystine storage. Mediators include PKC ∂, AMP Kinase and Caspase 4. Are there other mediators and/or modulators of this process?

3. The primary question that must be addressed is how does isolated lysosomal cystine interact with the 10mM GSH in the cytosol to yield an abnormal redox state? The existent data on abnormal redox potential in cystinotic cells give conflicting results. Are these the result of differing systems and assays? How does stored cystine affect the cytosolic redox state?

4. Do cystine crystals promote chronic renal interstitial fibrosis? Could improvement after bone morrow transplantation be secondary to the replacement of renal cystinotic histiocytes with wild-type cells?

5. Do other functions of cystinosin that are not related to cystine lysosomal transport explain the Fanconi syndrome and its unresponsiveness to cysteamine?

6. Does bone morrow transplantation represent a valid treatment option in humans? What are the mechanisms that mediate the observed effects in animals? Will these same mechanisms work in humans? Should the approach involve gene therapy or the use of HLA identical bone morrow?

2. Diagnostics and biochemical follow-up

1. Is it feasible to perform pre-symptomatic screening of cystinosis? *In utero* and in newborns?
2. What is the optimal technique for white blood cell (WBC) isolation and storage?
3. What is the optimal technique for WBC cystine measurement, including timing of the measurement?
4. Are there alternatives to WBC cystine measurements to monitor cysteamine treatment (plasma cysteamine, others)?
5. What is the role of cystine as a biomarker and cysteamine blood levels as a surrogate?
6. Can we measure crystal loads?
7. Is genetic diagnosis mandatory?
8. Is urine analysis helpful to raise the suspicion or make the diagnosis?
9. What other biochemical monitoring should be undertaken in treated patients?
10. What are the major clinical hints, providing high index of suspicion to diagnose cystinosis as early as possible?
11. What is the final decision regarding carnitine supplementation for patients post transplant? Is therapy worth the cardiovascular risk?

3. Management of infants and children with cystinosis

1. How to manage challenging nutritional issues in cystinosis?
   Tube feeding
   Vomiting
   Caloric recommendations
   Carnitine
   Copper, zinc status
   Vitamins

2. Management of polyuria
   Indomethacin
   Bladder function
   Monitoring urine volume

3. When/how to use growth hormone?

4. Management of electrolyte losses in Fanconi Syndrome
   Salt supplementation
   Calcium and phosphate homeostasis
   Hypokalemia
   Acidosis

5. When and how to introduce cysteamine therapy?
   Timing
   Dose
   Monitoring
   PPI
   Slow release cysteamine

6. Management of eye disease
   Eyedrops/side effects
   Compliance
   Long acting formulation

7. Management of thyroid disease
   Is there a critical TSH level to commence replacement?

8. Management of early neurologic manifestations
   Learning disorders
   Raised ICP

9. Management of progressive renal failure
   ACE inhibitors for proteinuria
   LRD transplantation and heterozygous donor (parent) issue
   Pre-transplant nephrectomy

10. Any required measures to enhance care for cystinosis in developing nations given the existing gap as compared to developed nations?

4. Adolescent issues

1. How to manage halitosis?
2. Is the bone disease of cystinosis in infancy replaced by another?
3. How should social adaptation of cystinosis patients be supported?
4. Can cystinosis patients perform all jobs? Is there an effect of neural disease on job training and performance?
5. Is there a special adaptation of therapeutic education and psychological back-up to adolescents
6. Is there a preference for a particular form of RRT in cystinosis patients?
7. Should cysteamine dose be adapted in patients on RRT? Optimal dose recommendations?
8. How should the onset of the need for a kidney transplant impact substrate reduction therapy?
9. Do cystinosis patients need a special preparation to renal transplantation?
10. Do cystinosis patients need different immunosuppressive therapy after renal transplantation?
11. How should cystinosis patients be prepared for the transition to internal medicine clinics?
12. How should pediatrician and adult teams be prepared for the transition to internal medicine clinics?
13. How should the recognition of systemic disease impact the therapeutic approach?

5. **Adult patient issues and the management of extra-renal manifestations of cystinosis**
    1. What is the chronology of organ dysfunctions in adults with cystinosis and which are amenable to substrate depletion therapy?
    2. What is the impact of early treatment with cysteamine on the onset of extra-renal complications?
    3. What is the optimal cysteamine dose in adult cystinosis patients?
    4. Is there evidence for life-time therapy with substrate-depleting agents?
    5. What are the adherence issues for cysteamine treatment?
    6. How to address the issues of family planning and male fertility?
    7. How to manage neurological complications of cystinosis?
    8. How to manage cystinosis myopathy, including growth hormone?
    9. What is the optimal multi-disciplinary follow-up of cystinosis patients?
    10. Who are the relevant physicians-specialists to participate in cystinosis clinics?
    11. Which are the specificities of late-onset form of cystinosis?

Overall for Conference Chairs to address: What is the role of a global registry in advancing clinical trials/research for cystinosis?