OPENING REMARKS

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Why Study “Rare Diseases”

NIH Director, Francis Collins

- 25 million Americans affected with 6000 rare diseases
- Only ~ 200 rare diseases have treatments
- Bridge molecular understanding into Rx
- Repurposing of Drugs
Why Have a Controversy Conference on Cystinosis

- Increase awareness to the professionals
- Increase awareness to those affected
- Coalesce anecdotal experiences
- Promote worldwide databases
- Improve outcomes

- Bridge gap from molecular etiology to patient-centered outcomes
- Provide a framework for investigations and trials going forward
- Increase the patient-professional relationships
The spectrum of clinical uncertainty

- Disease condition recognized and defined pathologically
- Animal studies, physiological explanation, laboratory evidence
- Observational population studies, epidemiological evidence
- Well designed clinical trials or a systematic summary of the evidence

Mechanism for Disease hypothesized

Hypotheses generated

Bias

Highest opportunity for introduction of bias into conclusions

Hypotheses proven or not

Highest degree of uncertainty

Lowest degree of uncertainty

KDIGO Cystinosis Conference | December 11-13, 2014 | Lisbon, Portugal
The Natural History of Cystinosis has Changed

Preserved GFR
Poor tubular Fx

But Why Exactly?
The Natural History of Cystinosis has Changed
Nephropathic Cystinosis Is a Systemic Disease


Adapted by Langman, 2014
Methods of this Controversy Conference

- Workgroups based on sub-topics
  - Basic & Translational Science
  - Optimal Diagnostics
  - Infant & Young Child
  - Adolescent
  - Adult Years
- Topic Lectures from our Experts
- Deliberations to help ‘crystallize’ the areas of known and unknown
- Presentations & Group Discussions to refine consensus
- New deliberations to further define what we don’t know.
Rules

- Listen to your colleagues.
- Contribute your deep knowledge.
- Work towards consensus.
- Accept some disagreements.

- Think creatively.
- Act with both passion and reason.
- Remember the scientific method.
- Think in a patient-centered manner.
What we are Not!
As We Begin

• We give many thanks to KDIGO
  – John Davis
  – Tanya Green, Michael Cheung, Danielle Green
• We give many thanks to our subgroup leaders
• We give many thanks to our professional participants
• We give many thanks to our lay participants
• We give thanks to friends who could not join us
• We give many thanks to our patients who teach us so much!
Nephropathic Cystinosis
from History to Future

Elena Levchenko, MD, PhD

University Hospitals Leuven
Katholieke Universiteit Leuven
Belgium
E. Levchenko performed consultancy for Raptor Pharmaceutical.
Cystine: first described amino acid

The first cystine stone found in a 36-year-old male patient with cystinuria (weight 18 g)

Thomas, K. et al. (2014) Cystinuria—a urologist’s perspective

First description of cystinosis

Abderhalden E.
Familiäre Cystindiathese.
Z. Physiol Chem 38: 557-561, 1903

Autopsy of a 21-months-old child:

- Failure to thrive
- Cystine crystals in the liver and spleen
- Confusion between cystinuria and cystinosis
Clinical presentation of cystinosis

- **Lignac G**: Über storung des cystinstoffwechsels bei kindern
  *Deutsch Arch Klin Med* 145: 139, 1924

- **deToni G**: Remarks on the relation between renal rickets (renal dwarfism) and renal diabetes
  *Acta Paediatr* 16: 479, 1933

- **Debré R et al**: Rachitisme tardif coexistent avec une néphrite chronique and glucosurie
  *Arch Méd Enf* 37: 597, 1934

- **Fanconi G**: Der nephrotisch-glykosurische zwergwuchs mit hypophosphhtämischer rachitis
  *Dtsch Med Wochenschr* 62: 1169, 1936
Biochemical basis of cystinosis

Schneider J et al.
Increased cystine in leukocytes from individuals homozygous and heterozygous for cystinosis

Science 157: 1321, 1967

Jerry Schneider “A personal History of Cystinosis” KDIGO 2014

Bone marrow aspirate from 5 m old cystinosis patient. Seen unstained with phase microscopy.
Altered lysosomal cystine transport in cystinosis

Steinherz R, Tietze F, Gahl WA, Triche TJ, Chiang H, Modesti A, Schulman JD.
Cystine accumulation and clearance by normal and cystinotic leukocytes exposed to cystine dimethyl ester
Proc Natl Acad Sci U S A. 1982, 79 : 4446

Jonas AJ, Greene AA, Smith ML, Schneider JA
Cystine accumulation and loss in normal, heterozygous, and cystinotic fibroblasts
Proc Natl Acad Sci U S A. 1982, 79 : 4442
Cysteamine depletes intra-cellular cystine accumulation

Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA
Cysteamine treatment protects renal function

Markello TC, Bernardini IM, Gahl WA.
Improved renal function in children with cystinosis treated with cysteamine
_N Engl J Med._ 1993, 1157
Genetic basis of cystinosis: *CTNS* gene


A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis.

*Nat Genet. 1998, 18:319*
Molecular basis of cystinosis: cystinosin

Kalatzis V, Cherqui S, Antignac C, Gasnier B.
Cystinosin, the protein defective in cystinosis, is a H(+)‐driven lysosomal cystine transporter.
EMBO J. 2001, 20: 5940
PubMed hits on cystinosis

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CONTROVERSIES IN
NEPHROPATHIC CYSTINOSIS
Improving the Future