ERKNet

The European Rare Kidney Disease Reference Network

Cystinosis: an update

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European Reference Networks

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Disclosures

E. Levtchenko performs consultancy for Orphan Europe, Chiesi, Kyowa Kirin, Advicenne and was supported by a research grant from Horizon Pharma

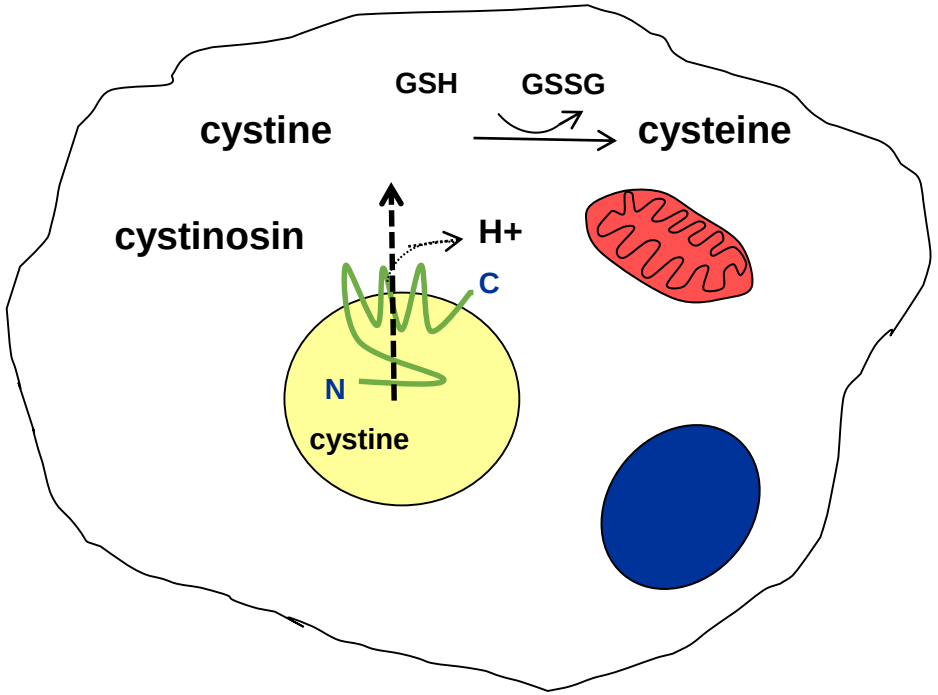
Overview of the lecture

- Introduction
  - biochemical and genetic basis of cystinosis
- Insights into pathogenesis of cystinosis
- Diagnosis of cystinosis
- Treatment of cystinosis
  - cysteamine treatment
  - novel therapies
- Take home messages

Cystinosis

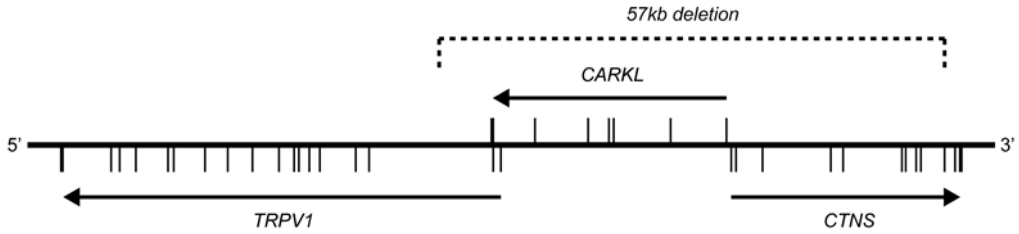
- An autosomal recessive disease caused by lysosomal accumulation of cystine due to defective exodus of cystine out of the lysosomes
- Incidence ~1:100,000 - 200,000 newborns (clustering in some populations)
- Most common cause of inherited generalized proximal tubular dysfunction (renal Fanconi syndrome) progressing to end stage renal disease (ESRD)

Lysosomal cystinosin (*CTNS*, 17p13) is mutated in cystinosis



Town et al. Nat Genet 1998
Attard et al. Hum Mol Genet 1999
Kalatzis et al. Hum Mol Genet 2004
Levtchenko et al. Eur J Hum Genet 2014

Most common mutation in North European population: 57 kb deletion



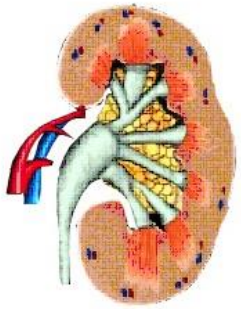
> 140 other mutations described (David et al. 2019)

- Mutation detection rate > 95%:
  Nonsense, missense, splice-site, promotor, micro-deletions, duplications
- Genotype – phenotype correlation: severe mutations → severe phenotype

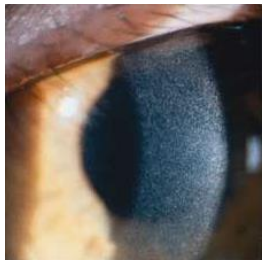
Clinical forms

Nephropathic cystinosis

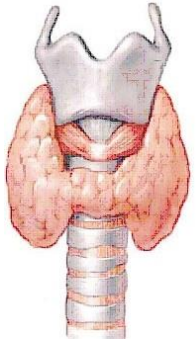
- **Infantile form (>90%):**
  - Fanconi syndrome ~ 3-6 months
  - end stage renal disease (ESRD) ~ 10 years
- “**Late-onset**” **(juvenile) form (~5%):**
  - later onset (often during puberty)
  - mild tubulopathy, more pronounced proteinuria
  - later progression to ESRD
- **Ocular form**



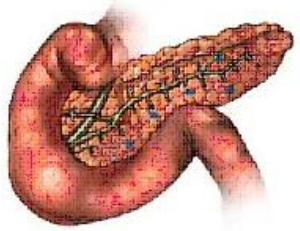
Fanconi syndrome
Renal failure



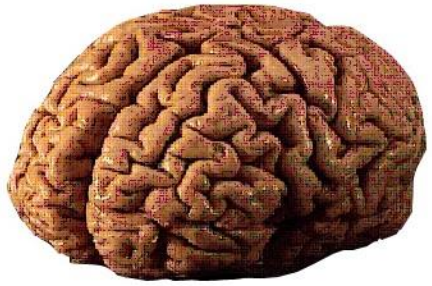
Photophobia
Keratopathy
Retinopathy



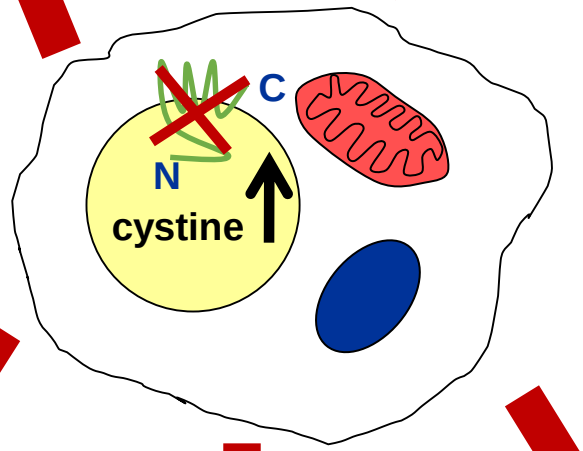
Hypothyroidism

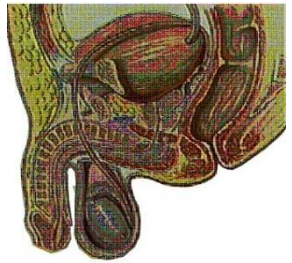


Diabetes
Exocrine pancreas deficiency

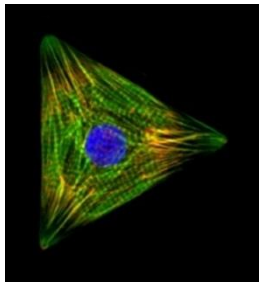


Cerebral atrophy
Neuro-cognitive deficits
Pyramidal symptoms
Stroke-like episodes

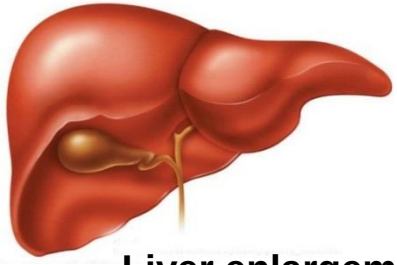




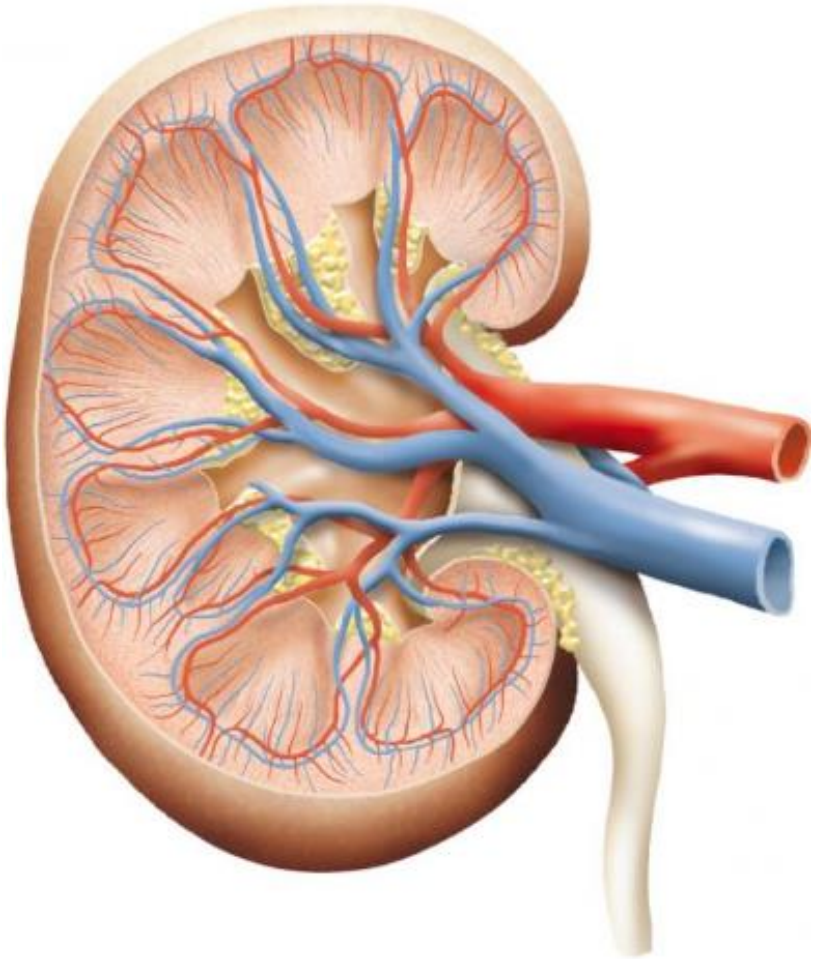
Delayed puberty
Male infertility



Muscular wasting



Liver enlargement, fibrosis



Kidney is the first organ affected by cystinosis

Pathogenesis of kidney disease in cystinosis

Podocyte disease:
glomerular proteinuria, FSGS

Proximal tubule (PT) disease:
renal Fanconi syndrome

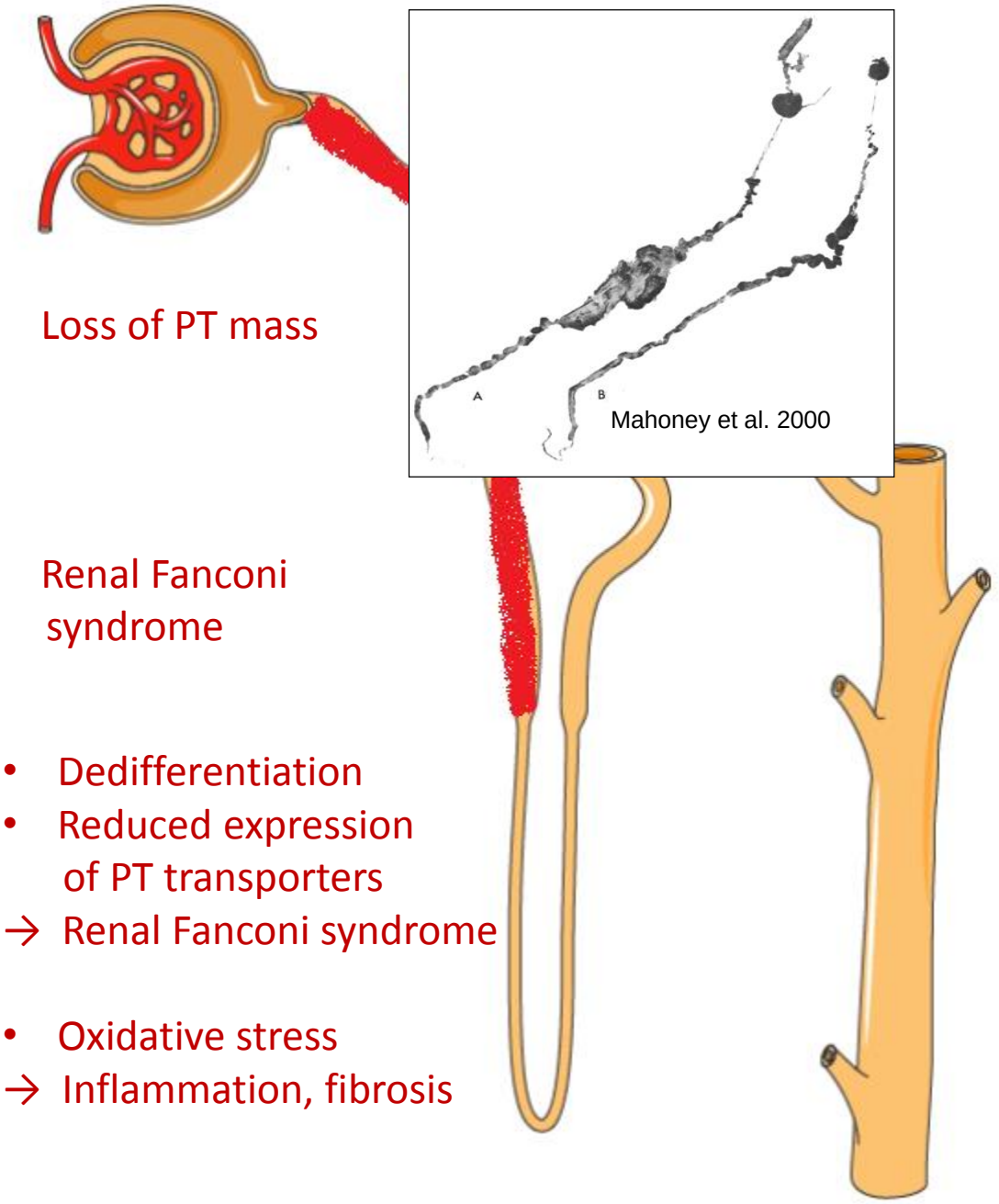
Renal interstitial inflammation and fibrosis:
progressive CKD

Proximal tubule (PT) dysfunction

- Loss of PT cells into urine
  (Ivanova et al. 2016)
- PT cell apoptosis
  (Park et al. 2002, 2006; Gaide Chevronnay et al. 2014)

- Impaired mitochondrial function & oxidative stress & ↓ mit cAMP
  (Baum 1998, Wilmer et al. 2011, Bellomo et al. 2018)

- Impaired vesicle trafficking & autophagy
  (Sansanwal et al. 2010, Raggi et al. 2014, Gaide Chevronnay et al. 2014, Ivanova et al. 2015, Rega et al. 2016, Zhang et al. 2017, Festa et al. 2018)



- Loss of PT mass

- Renal Fanconi syndrome

- Dedifferentiation
- Reduced expression of PT transporters

→ Renal Fanconi syndrome

- Oxidative stress

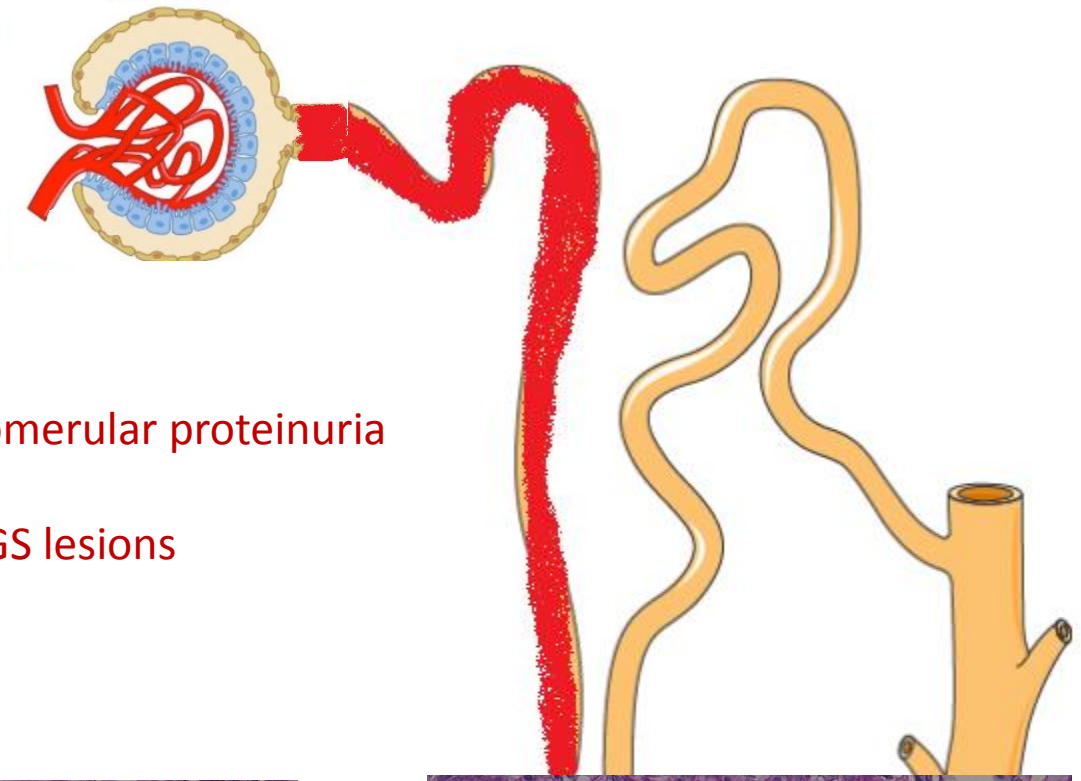
→ Inflammation, fibrosis

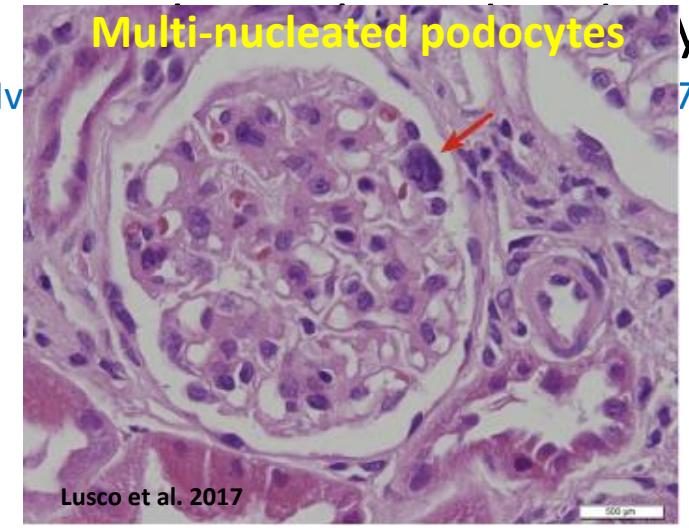
Podocyte dysfunction

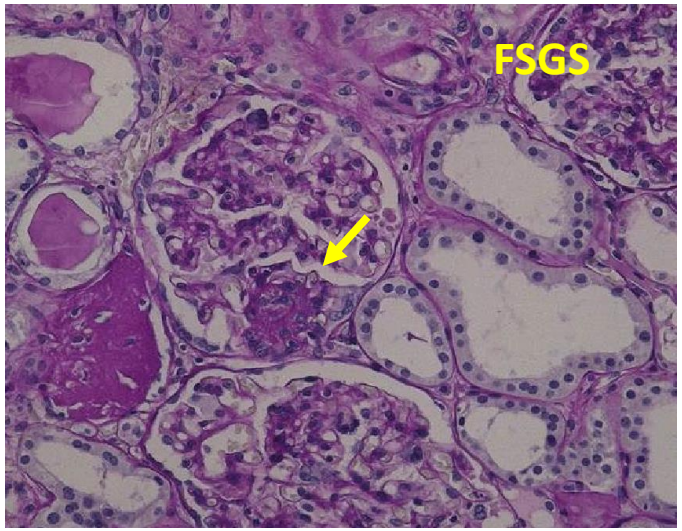
- Loss of podocytes into urine
  (Ivanova et al. 2016)
- Increased podocyte motility and decreased adhesion in vitro
  (Ivanova et al. 2016)
- Morphologic podocytes changes
  - Podocyte foot process effacement
  - ytes

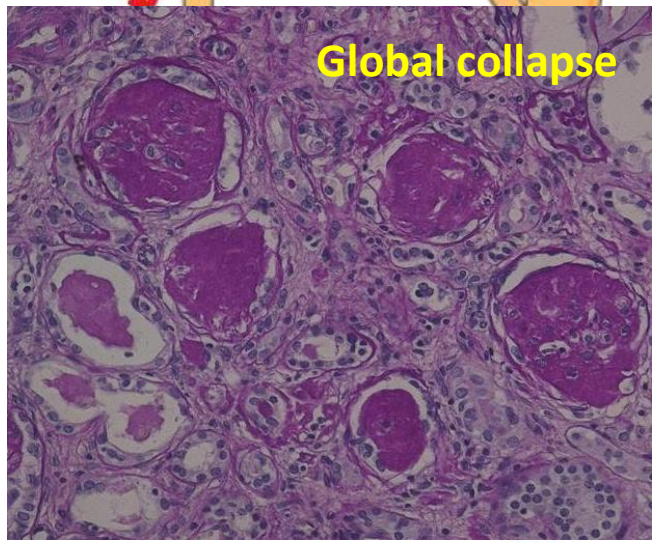
(Iv 7)

- Glomerular proteinuria
- FSGS lesions

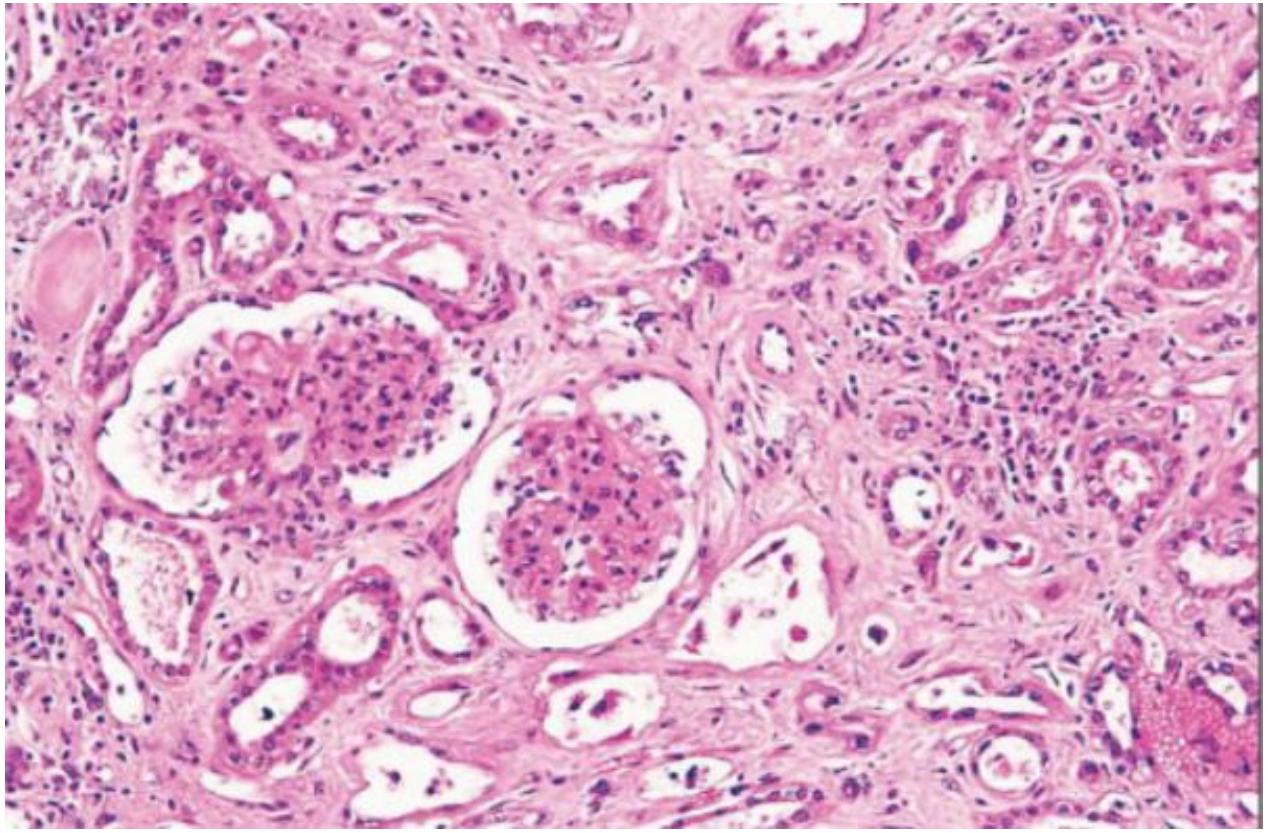








Renal interstitial inflammation and fibrosis



- Cystine crystals are mainly located in renal interstitium (free or in histiocytes), and rarely in PT cells or podocytes

- Inflammasome activation by cystine crystals (increased expression of inflammasome-related genes Casp-1, Pycard, Il-18, Il18r1, Il1r1, Il1rl2):

→ production of pro-inflammatory cytokines and chemokines

→ renal interstitium inflammation and fibrosis

Prencipe et al. JASN 2014

Diagnosis of cystinosis

- **Suspected clinical presentation**
  - cystinosis - most common cause of Fanconi syndrome
  - unexplained eye complaints, photophobia
  - glucosuria & proteinuria (check for low molecular weight proteins)
- **Measurement of elevated cystine content in granulocytes:**
  - controls < 0.3 nmol ½ cystine/mg protein
  - heterozygotes < 1 nmol ½ cystine/mg protein
  - patients at diagnosis > 2 nmol ½ cystine/mg protein
  - patients on cysteamine therapy < 1 nmol ½ cystine/mg protein
  - values of your own laboratory!
- **Cystine crystals in cornea (>1 year)**
- **Molecular analysis of cystinosis gene**

Treatment of cystinosis

Management of renal Fanconi syndrome

- Free access to water and toilet, **avoid dehydration**
- Nutritional support 100-130% RDI
- Supplementation of electrolyte losses (Veys et al. Curr Opin Pediatr 2017):
  - (Na) K citrate 2-10 mmol/kg/day QID
  - Na bicarbonate 2-15 mmol/kg/day QID
  - K chloride 2-10 mmol/kg/day QID
  - Salty food, Na chloride is rarely required
- Treatment & prevention of rickets:
  - (Na) K phosphate 0.2-2 mmol P/kg/day QID
  - Alphacalcidol 0.2-2 µg/day QD
- Copper deficiency: copper 1-10 mg/day BID
- Severe polyuria: indomethacin 0.5-3mg/kg/day TID
- In patients with adequate metabolic control, but persistent poor growth:
  - rhGH treatment 0.045 mg/kg/day QD

Indomethacin treatment reduces urinary losses due to renal Fanconi syndrome

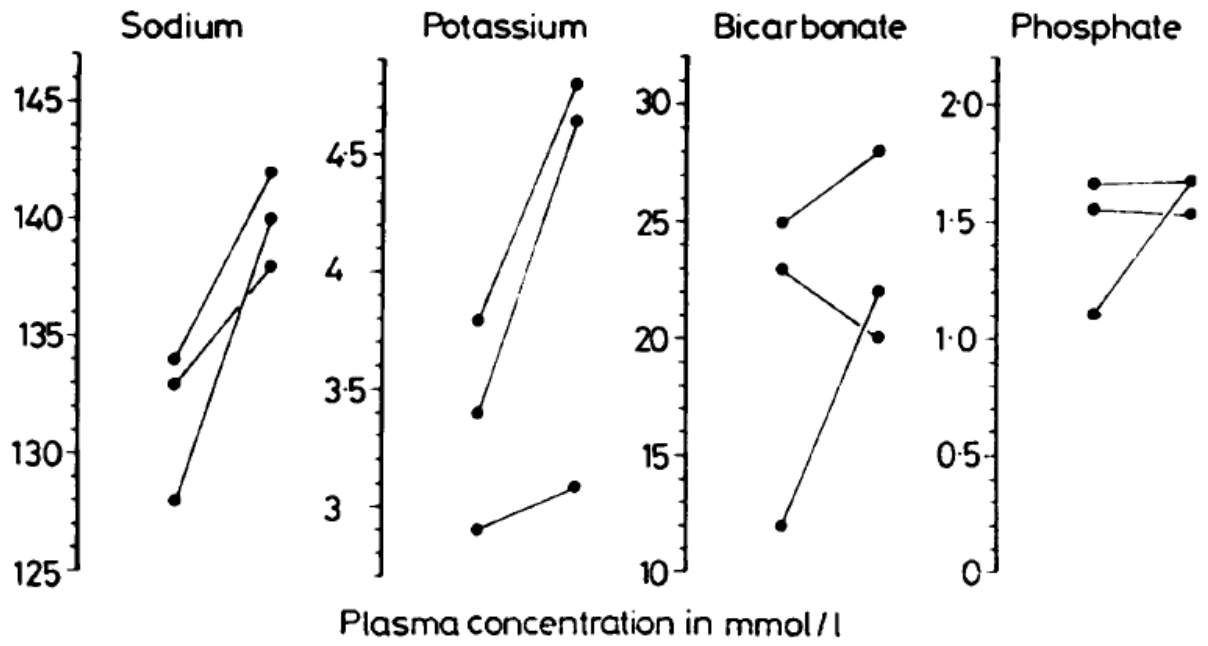
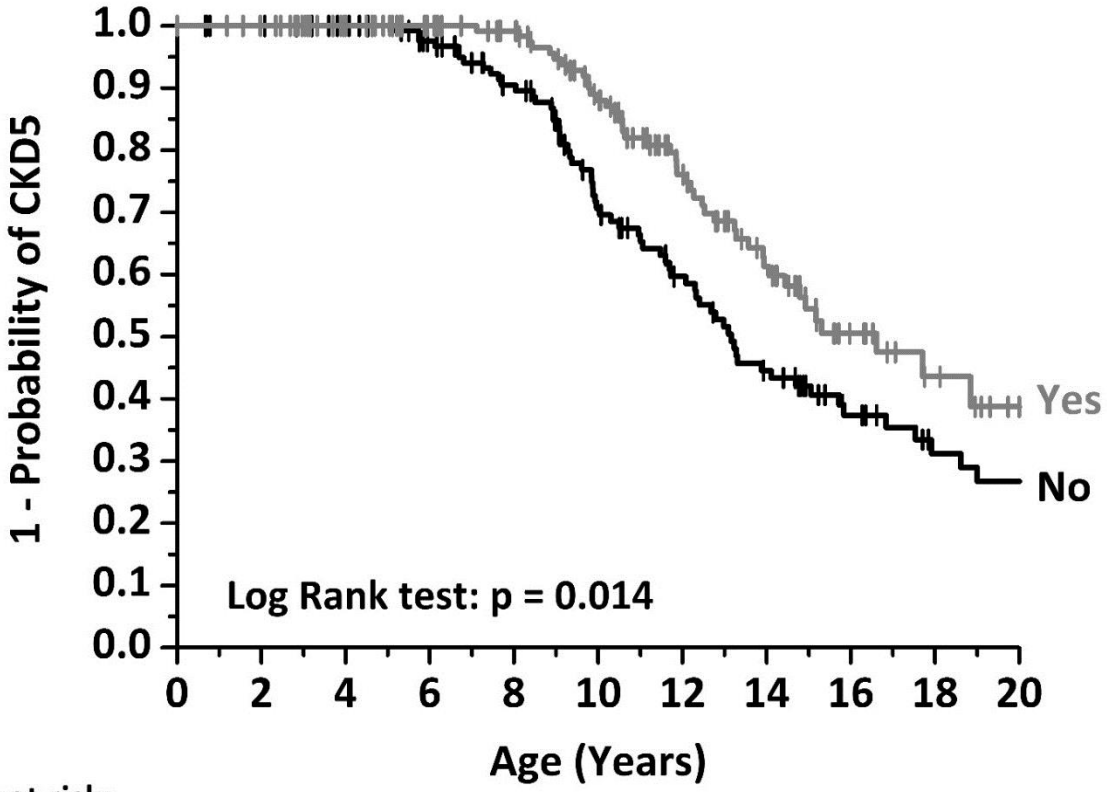


Fig. 3 ***Effects of 2 weeks' treatment with indomethacin on plasma electrolyte concentrations.***

Haycock et al. Arch Dis Child 1982

- Rational: increased urinary PGE + successful use of indomethacin in one child (Bétend et al. 1979)
- 3 children with cystinosis
- Dose: 2 mg/kg/day, 9-18 months
- Increased sodium reabsorption, reduced free water clearance, improved plasma concentrations of Na, K, bicarbonate, P
- No acceleration of kidney function deterioration

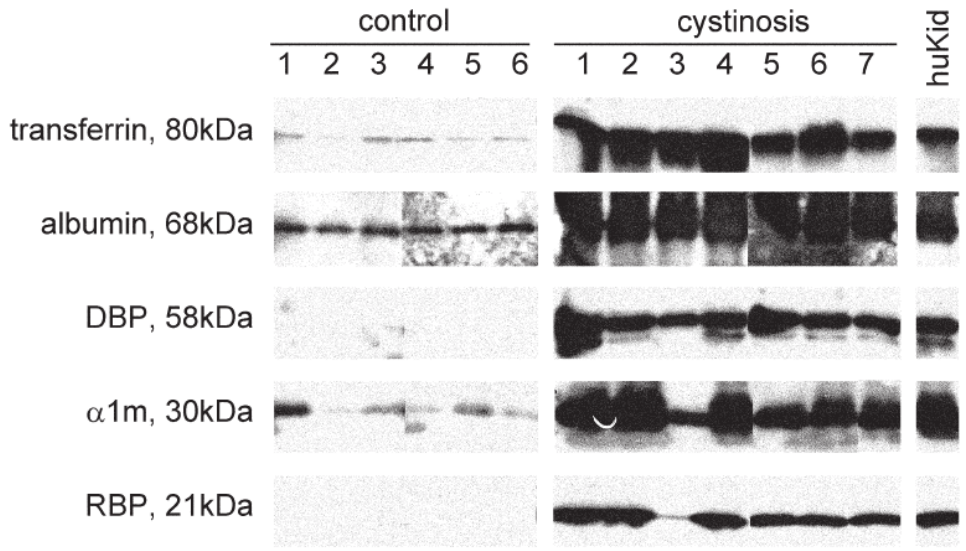
Probability of CKD5 depending on indomethacin use
(data from EUNEFRON cohort)



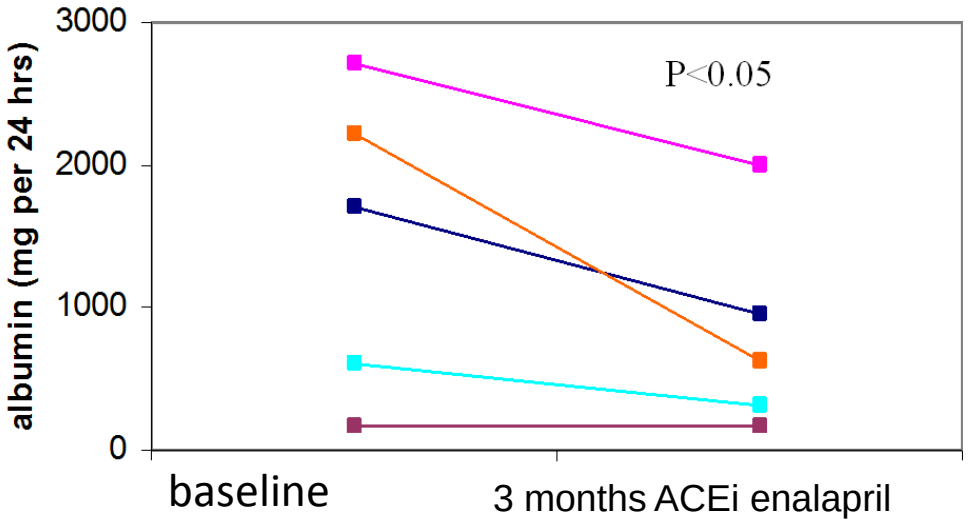
Number at risk:					
INDO: No	137	122	67	28	11
INDO: Yes	160	135	90	28	3

Slide Courtesy F. Emma

Anti-proteinuric treatment: use of ACE inhibitors



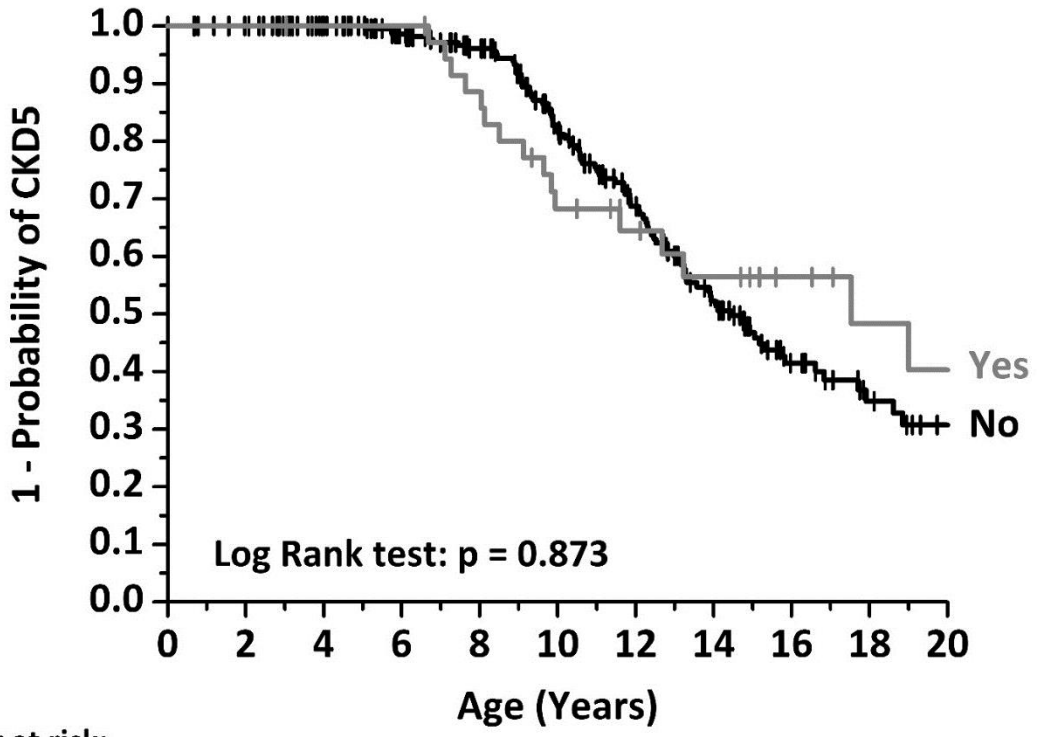
Wilmer et al et al. AJKD 2008



Levtchenko et al. Clin Nephrol 2003

Greco et al. Pediatr Nephrol 2010: use of ACE inhibitors decreased risk of chronic renal failure in cystinosis (H.R. 0.15 (95% C.I. 0.03-0.68))

Probability of CKD5 depending on ACEi use
(data from EUNEFRON cohort)



Number at risk:					
ACEi: No	261	222	135	45	10
ACEi: Yes	36	35	22	11	4

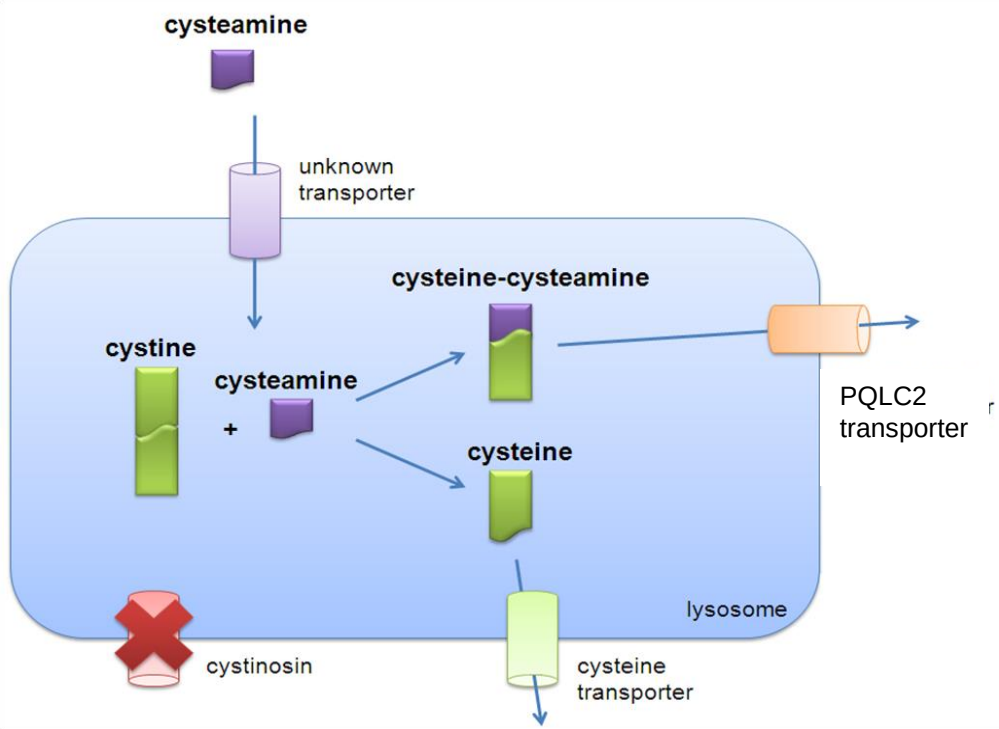
No information on:

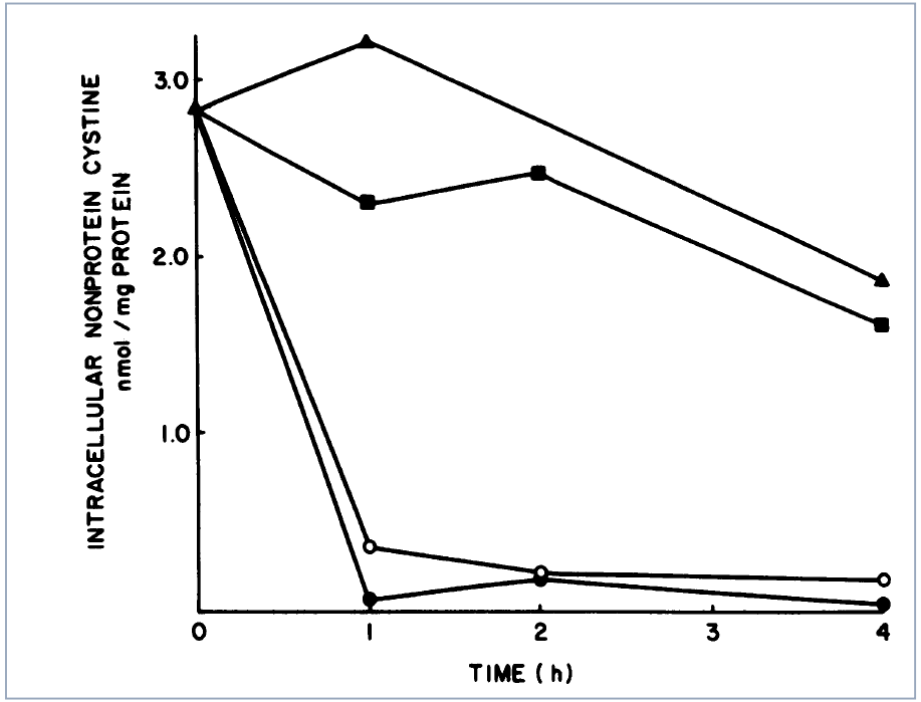
- dose
- duration
- anti-proteinuric effect

Avoid combination of indomethacin and ACEi!!

Slide Courtesy F. Emma

Cysteamine depletes intra-cellular cystine accumulation



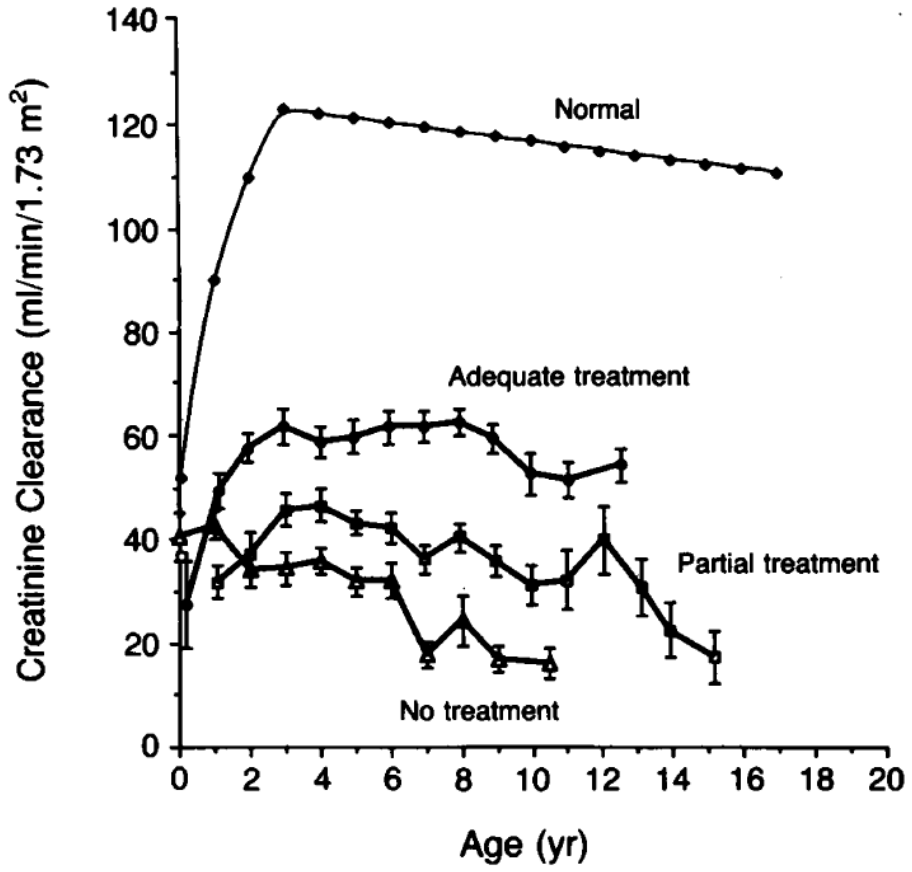


Cysteamine concentrations

- ● 1 mM
- ○ 0.1 mM
- ■ 0.01 mM
- ▲ control

Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA
Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo.
J Clin Invest. 1976, 58: 180

Cysteamine treatment improves kidney function survival



<u>Recommended dose</u>:
1.3 – 1.9 g/m²/day

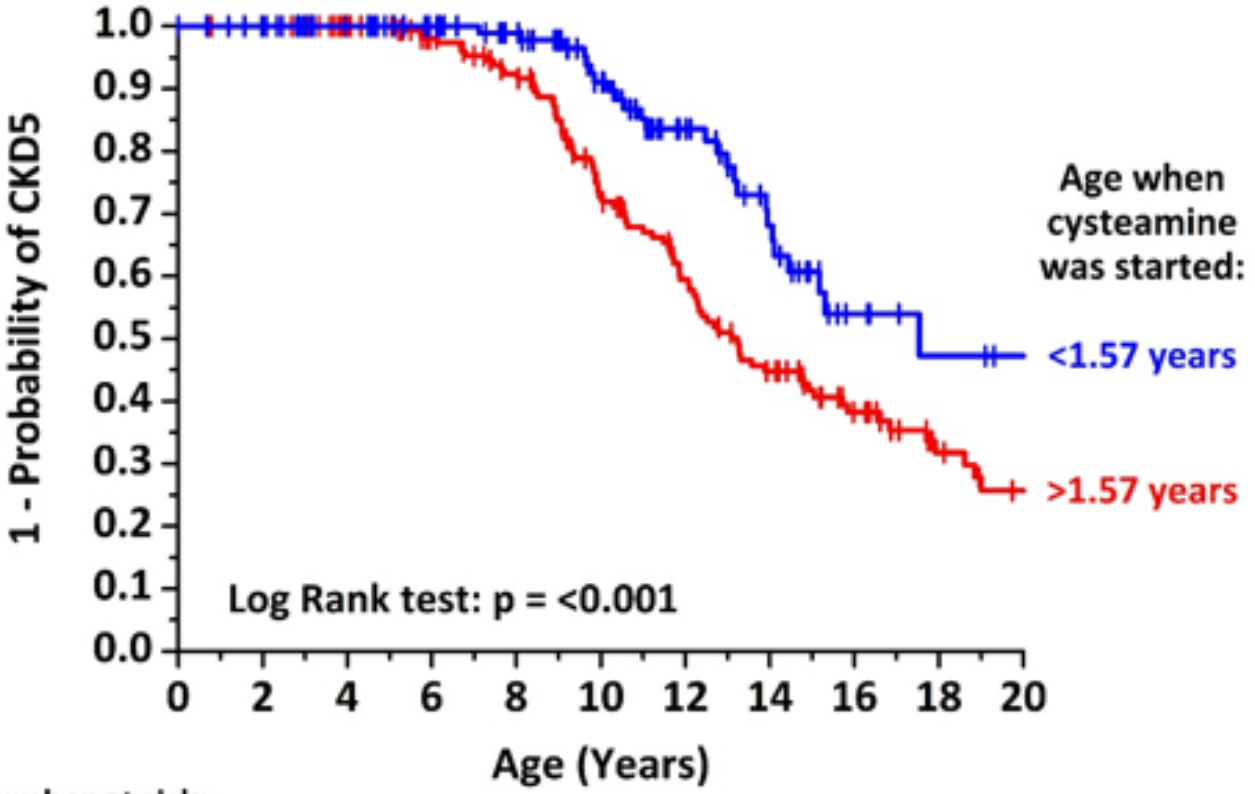
Divided in:
4 daily doses (Cystagon®)
2 daily doses (Procysbi®)

<u>Side effects:</u>
GI complaints
Bad breath and body smell

→ limiting compliance

Markello TC, Bernardini IM, Gahl WA.
Improved renal function in children with cystinosis treated with cysteamine
N Engl J Med. 1993 ,1157

Probability of CKD5 depending on age at start of cysteamine (data from EUNEFRON cohort)



Number at risk:					
< 1.57 years	124	102	65	18	4
> 1.57 years	173	155	93	38	10

Slide Courtesy F. Emma

Renal replacement therapy in cystinosis

• ESPN/ERA-EDTA 2016:	255/14,366	1.8%
• NAPRTCS 2008:	104/7,037	1.5%
• ANZDATA 2009:	4/369	1.1%

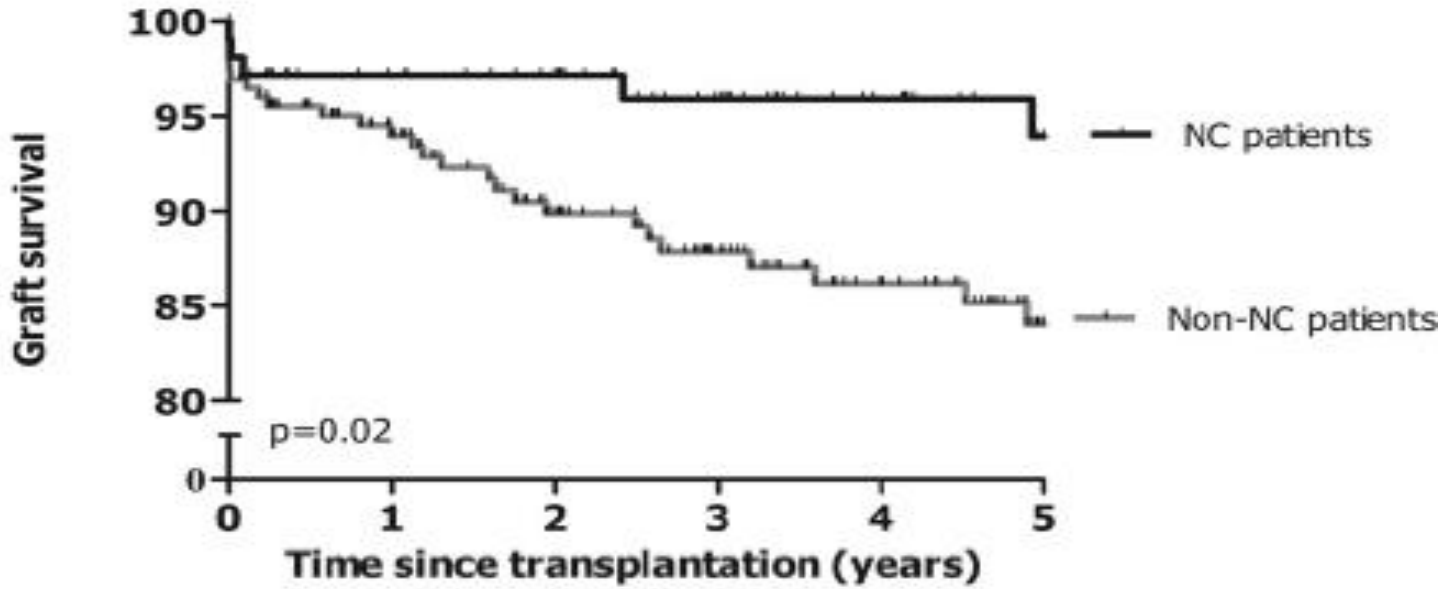
- Both peritoneal dialysis and hemodialysis are suitable for cystinosis patients
- No evidence that cysteamine dose adjustment is required in patients on dialysis (Besouw et al. 2011)
- Metabolism of cysteamine might be impaired in ESKD (communication C. Langman 2018)

Kidney transplantation in cystinosis

- Graft survival is excellent
- Nephrectomy of the native kidneys because of persistent polyuria is rarely required (Sharbaf et al. 2012)
- Immunosuppressive treatment is similar to non-cystinosis patients:
  - preference for steroid-free regimen
  - CAVE! diabetes due to steroid and tacrolimus treatment
- Disease doesn’t recur in kidney graft
- Parents are accepted as kidney donors
- Cysteamine treatment has to be re-started when patient can take oral medications after transplantation and continues life long

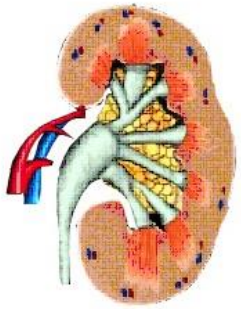
ESPN/ERA-EDTA Registry Report of Transplantation in Childhood Cystinosis

Van Stralen et al., *Clin J Am Soc Nephrol* 2011, 6:2485

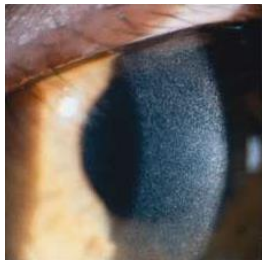


NC patients	122	92	85	71	56	47
Non-NC patients	235	175	144	117	94	67

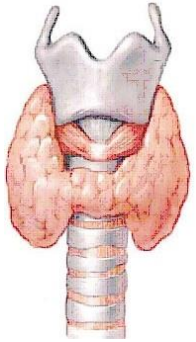
Figure 2. | Five-year graft survival of patients with nephropathic cystinosis (NC) and non-NC patients.



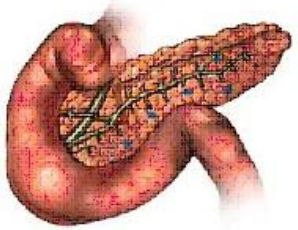
Fanconi syndrome
Renal failure



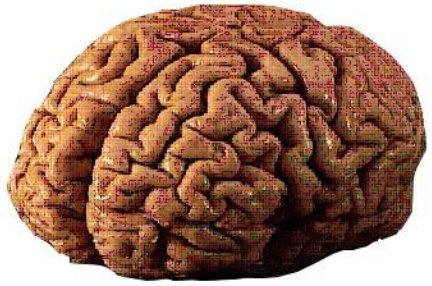
Photophobia
Keratopathy
Retinopathy



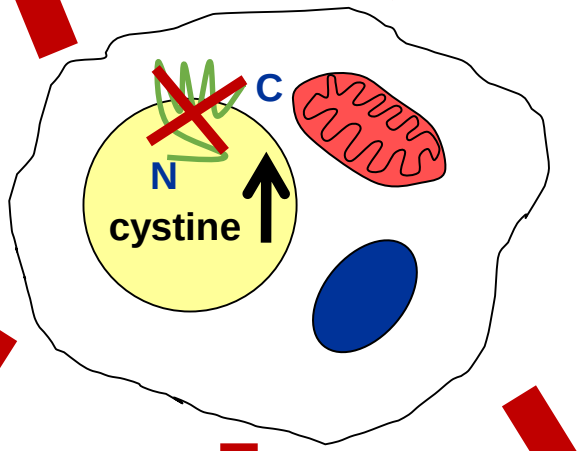
Hypothyroidism

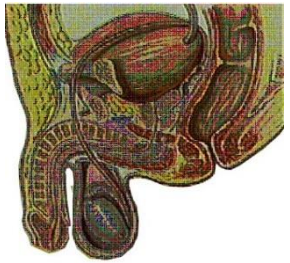


Diabetes
Exocrine pancreas
deficiency

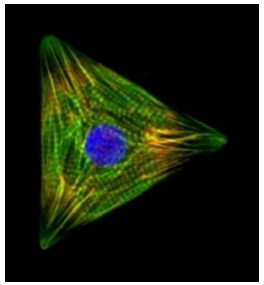


Cerebral atrophy
Neuro-cognitive deficits
Pyramidal symptoms
Stroke-like episodes

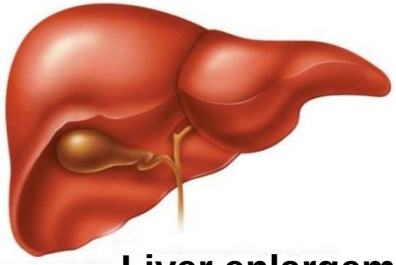




Delayed puberty
Male infertility



Muscular wasting

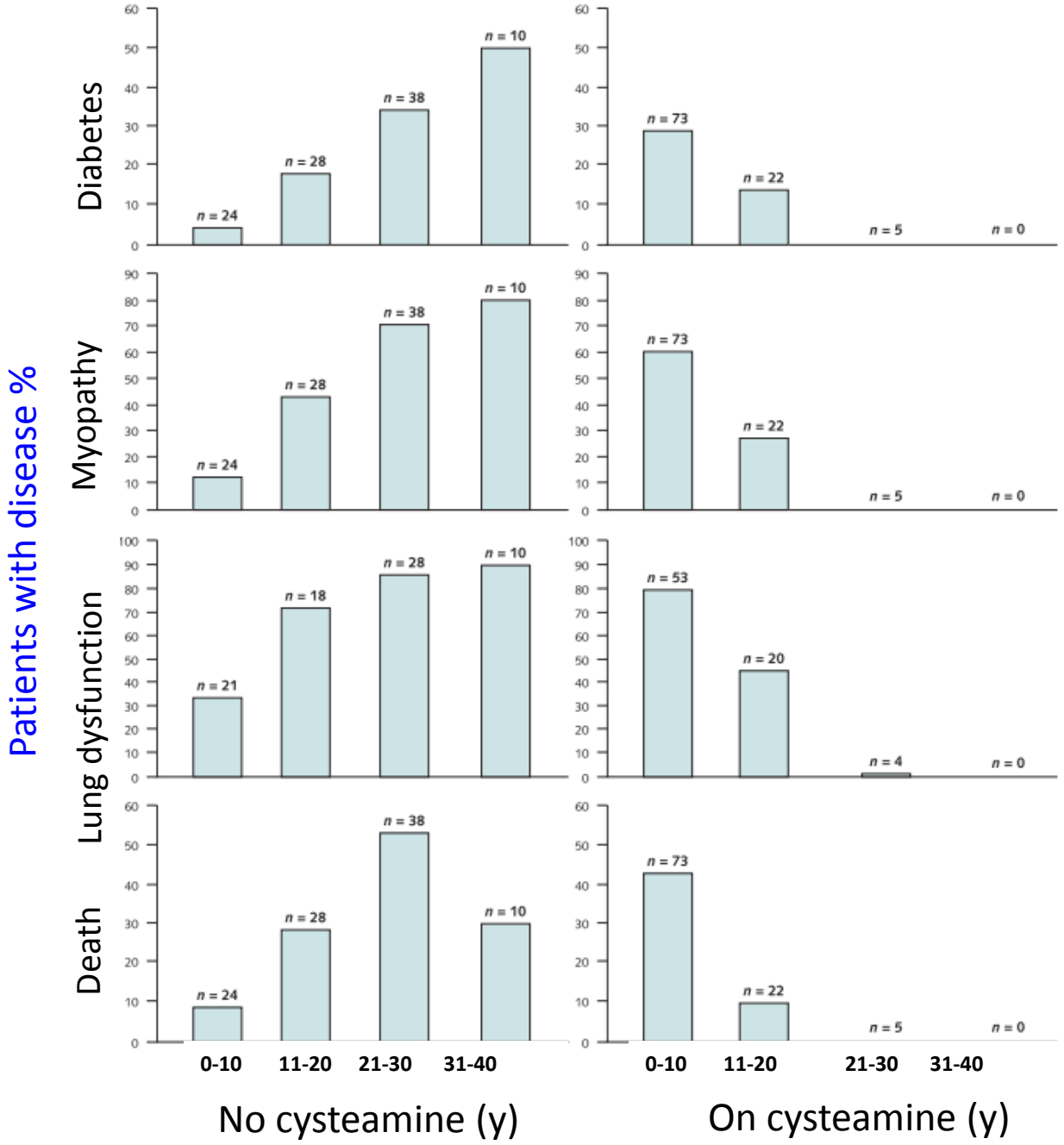


Liver enlargement,
fibrosis

Nephropathic Cystinosis in Adults: Natural History and Effects of Oral Cysteamine Therapy

Gahl et al., *Ann Intern Med. 2007;147:242-250*

Cysteamine treatment postpones or prevents extra-renal manifestations of cystinosis, prolongs life expectancy and should be continued after kidney transplantation

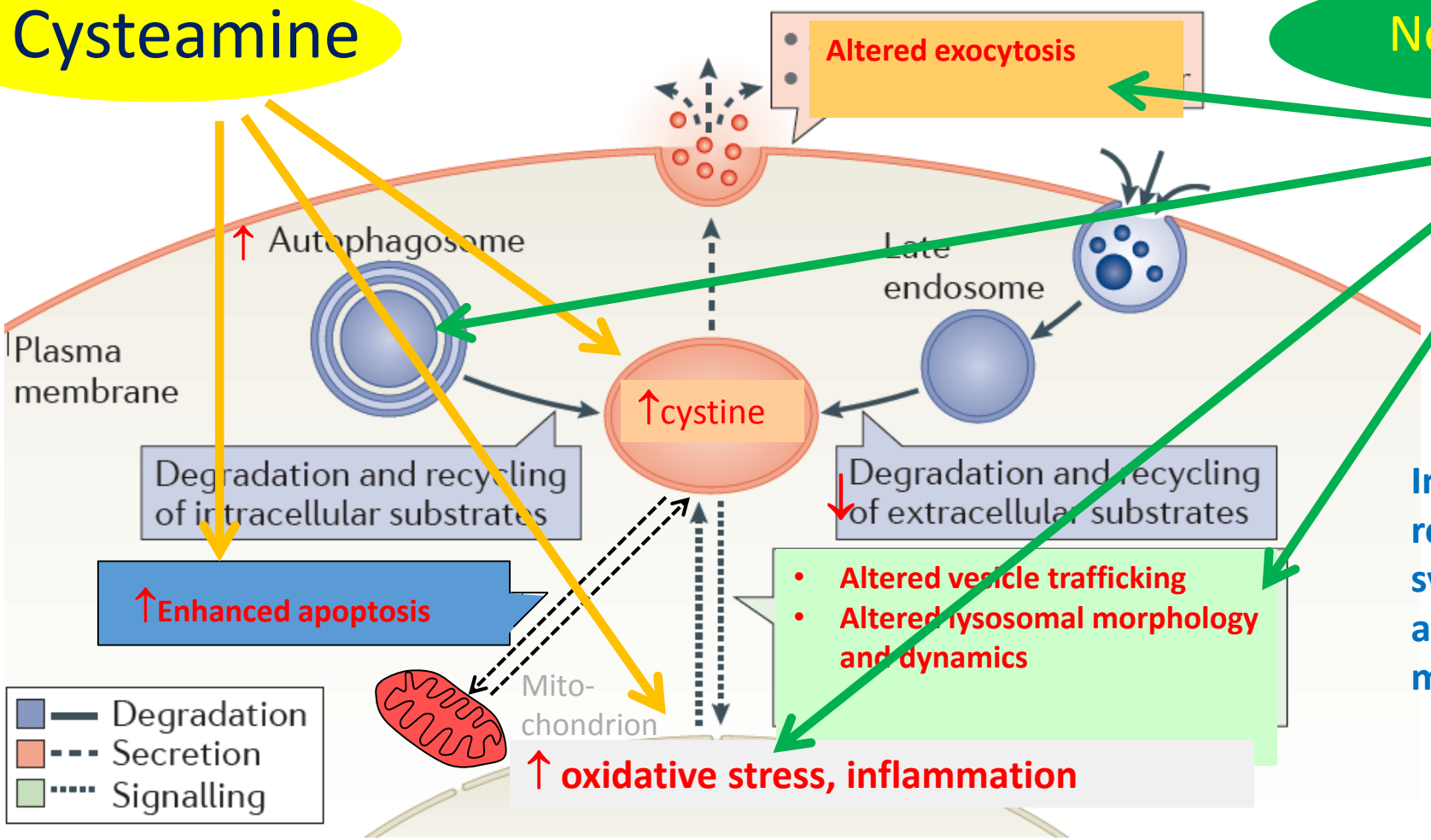


Novel therapies

Cysteamine

New drugs

Cysteamine has no effect on renal Fanconi syndrome



Improvement of renal Fanconi syndrome in vitro and in animal models

Adapted from Settembre et al. Nat Rev Mol Cell Biol. 2013

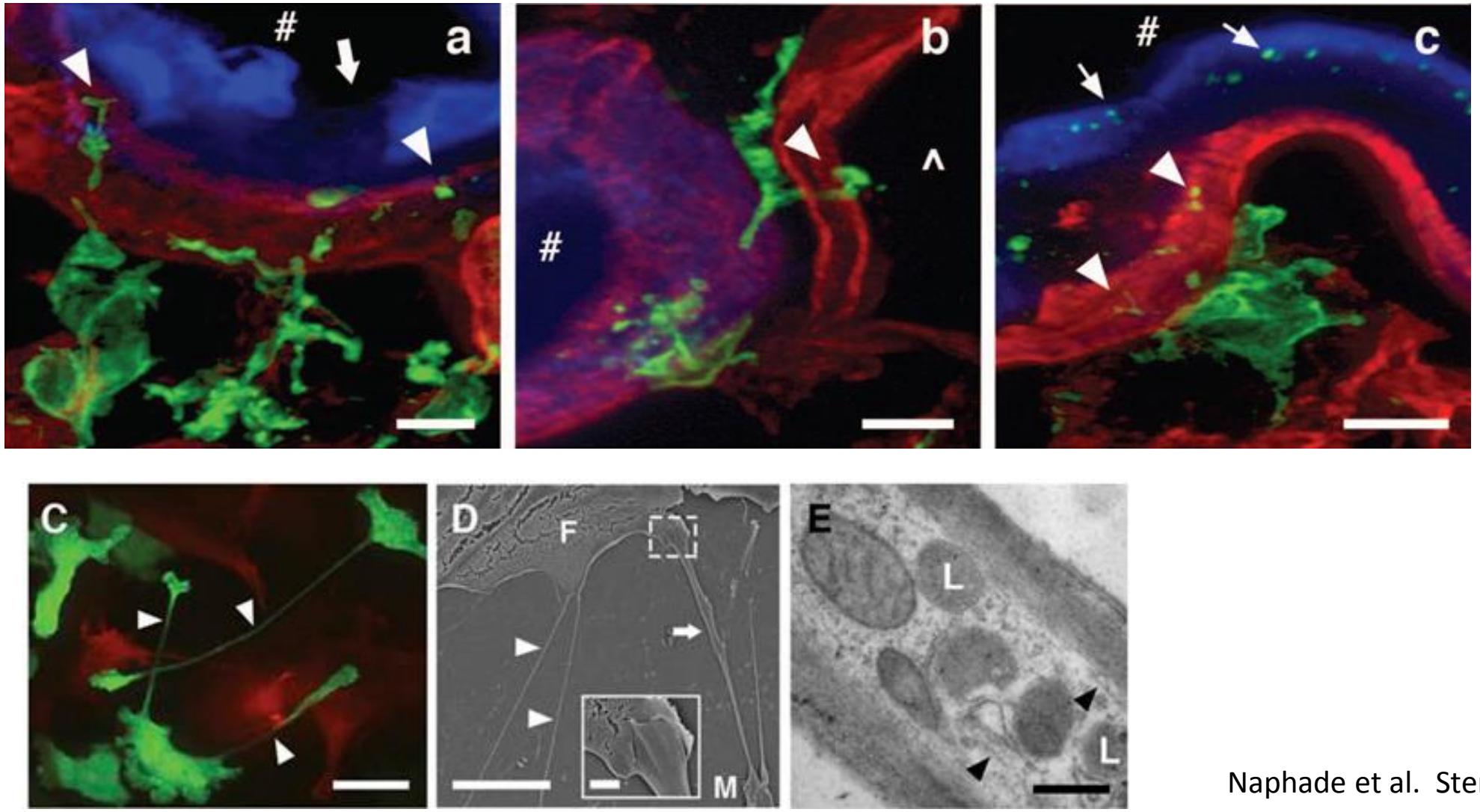
Hematopoietic stem cell (HSC) transplantation in cystinosis

- HSC transplantation (HSC Tx) is efficient in cystinosis mouse model

  (Syres et al. 2009, Yeagy et al. 2011, Harisson et al. 2013)
  - Decrease of cystine accumulation in different tissues
  - Preservation of kidney function on short and long term
    - Effect is dependent on efficiency of engraftment
  - Improves extra-renal complications (thyroid) (Gaide Chevronnat et al. 2016)

- Mechanism of action
  - Engraftment of HSC in interstitium of organs → differentiation into tissue macrophages → clearance of cystine crystals
  - Lysosomal cross correction via tunneling nanotubes between macrophages derived from HSC and epithelial cells of recipient

Effect HSCTx due to formation of the tunneling nanotubes between donor cells and recipient epithelial cells



Naphade et al. Stem Cell 2015

A Phase I clinical trial on stem cell gene therapy for cystinosis

NIH U.S. National Library of Medicine

ClinicalTrials.gov

S. Cherqui

Stem Cell Gene Therapy for Cystinosis

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03897361

Recruitment Status : Not yet recruiting
First Posted : April 1, 2019
Last Update Posted : April 5, 2019

See Contacts and Locations

Sponsor:
University of California, San Diego

Collaborators:
California Institute for Regenerative Medicine (CIRM)
Cystinosis Research Foundation

Information provided by (Responsible Party):
Stephanie Cherqui, University of California, San Diego

- Autologous HSC after lentiviral gene therapy to supplement CTNS
- Adults > 18 y.o.
- At least 1 year after kidney Tx

Allo-HSC Tx in cystinosis: clinical case (1)

Male patient with cystinosis (het 57kb deletion & c.926dup exon 11):

diagnosis at 2 years and 8 months

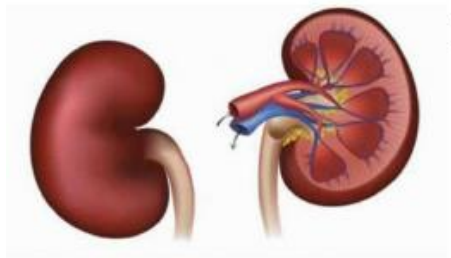
severe renal Fanconi syndrome, deterioration of kidney function

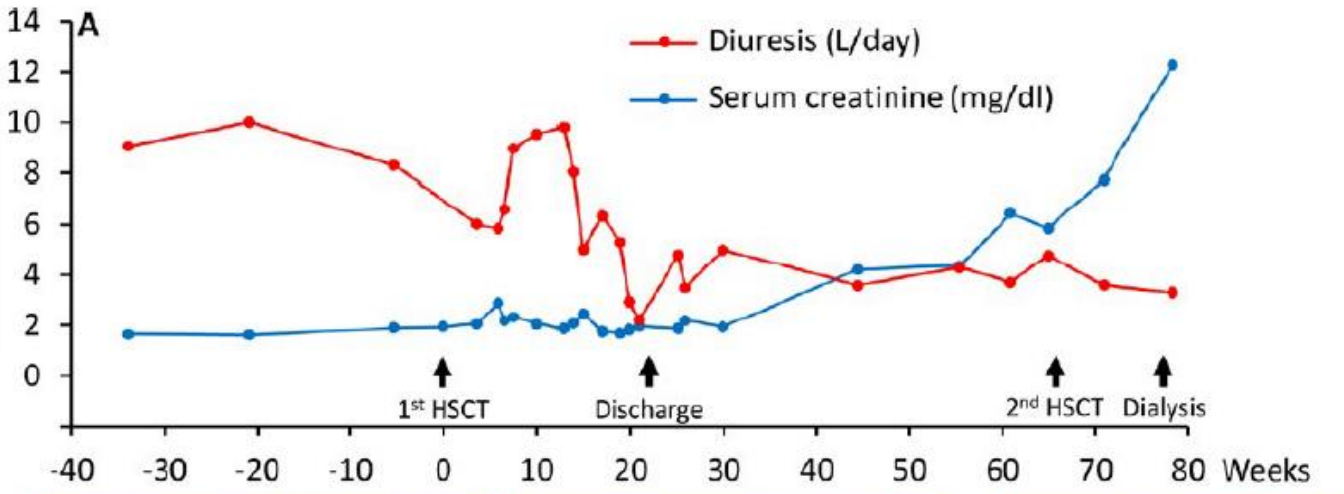
signs of cysteamine toxicity

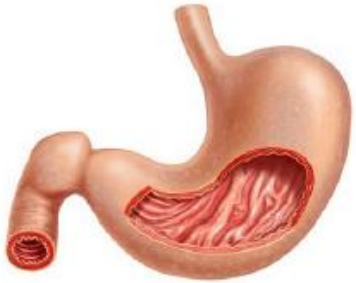
16 years of age

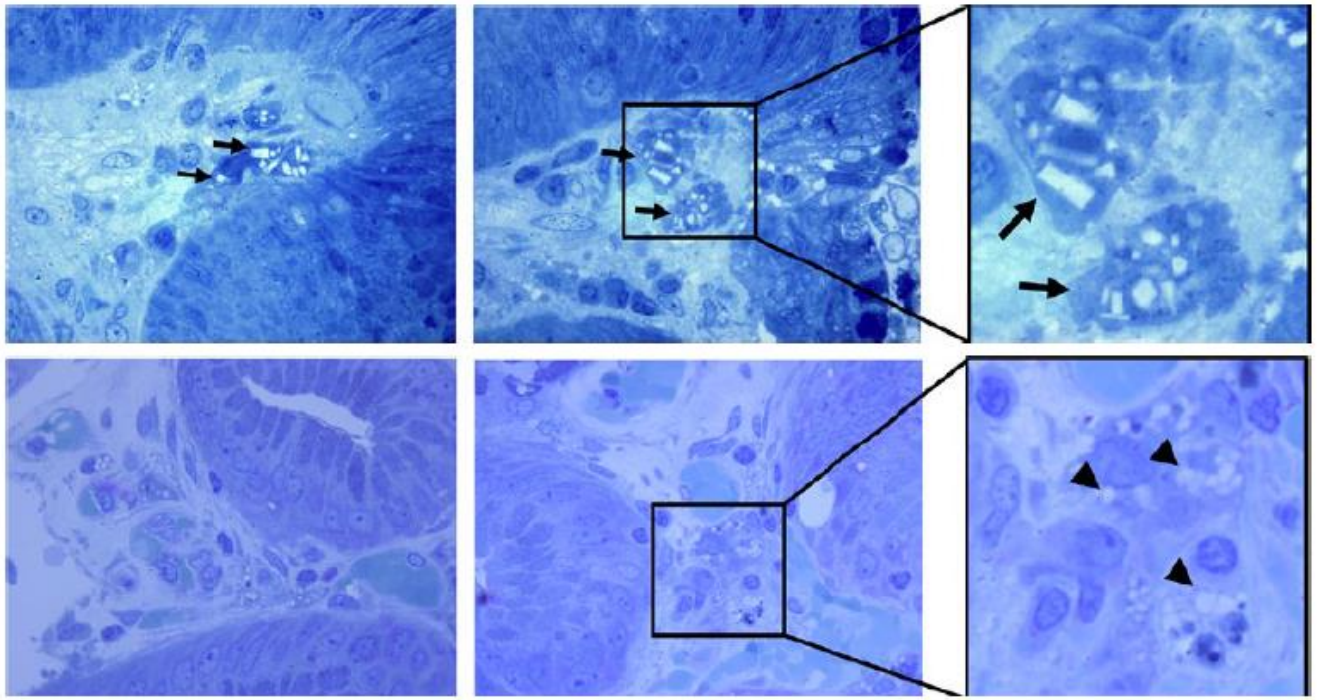
- Pre-HSCTx myeloablative conditioning (treosulfan, fludarabine, thiotepa, ATG)
- 7,88 x 106 CD34+ HSC/kg; 166 x 106 CD3 + T-cells/kg from 10/10 HLA matched donor
- Post - HSTCx GvHD prophylaxis (tacrolimus, MMF, MTX)
- 22 days post-HSCTx: engraftment (Filgrastim D16, D17, D19)
- Full donor chimerism (>95%) in BM up to 184 days after Tx, and in blood up to 462 days after Tx

Elmonem et al. AJT 2018





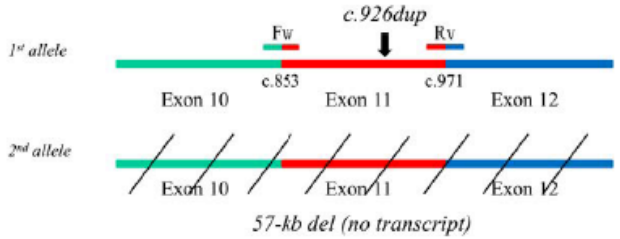




Elmonem et al. AJT 2018

Slide Courtesy K. Veys

Expression of WT CTNS in patient's tissues after Allo-HSC Tx (24-30 months)



CTNS mRNA expression

Pre-HSCT

Healthy: 100% WT *CTNS* allele

Patient: 100% mutant *CTNS* alle

Post-HSCT

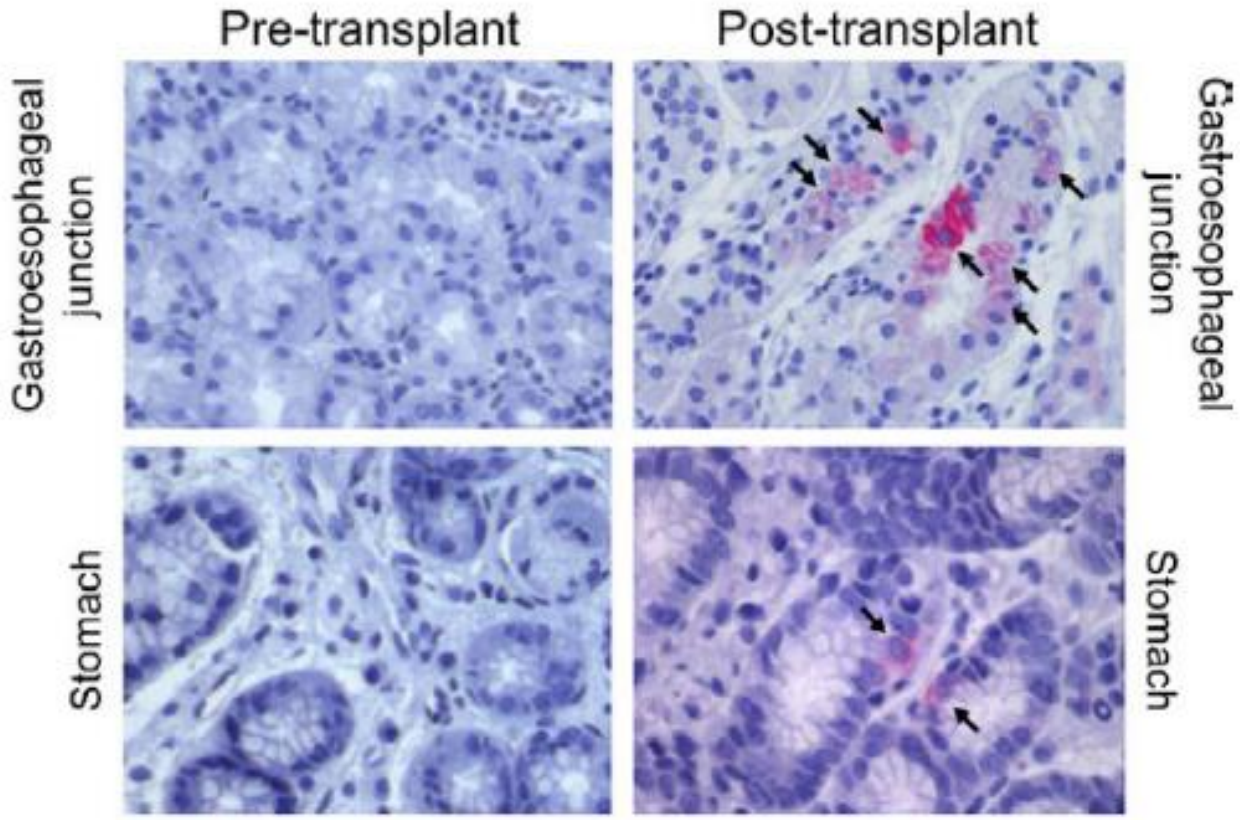
Healthy: 100% WT *CTNS* allele

Patient:

PTEC: 22% WT *CTNS* allele

Liver: 44% WT *CTNS* allele

Cystinosin-LKG protein expression



Elmonem et al. AJT 2018

Allo-HSC Tx in cystinosis: clinical case (2)

- Acute Graft-versus-Host Disease (GvHD)
- Central nervous system complications (central pontine myelinolysis, pyramidal syndrome, recurrent epileptic seizures, neurologic toxicity of multiple drugs)
- Partial graft failure (parvovirus B19): second HSC Tx from the same donor
- Therapy resistant chronic GvHD
- Death due to multi-resistant Pseudomonas infection

Elmonem et al. AJT 2018

Take home messages

- Diagnosis of cystinosis: high level of suspicion in patients with renal Fanconi syndrome or unexplained proteinuria and glucosuria
  - Eye examination (cystine crystals)
  - Cystine measurements in WBC, DNA test

- Treatment with cysteamine remains the main therapy
  - Early administration improves kidney function prognosis
  - Treatment should be continued after kidney transplantation to protect extra-renal organs

- Novel therapies are underway to clinical trials

  risk – benefit balance should be carefully considered

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Youth worker: C. Cooreman
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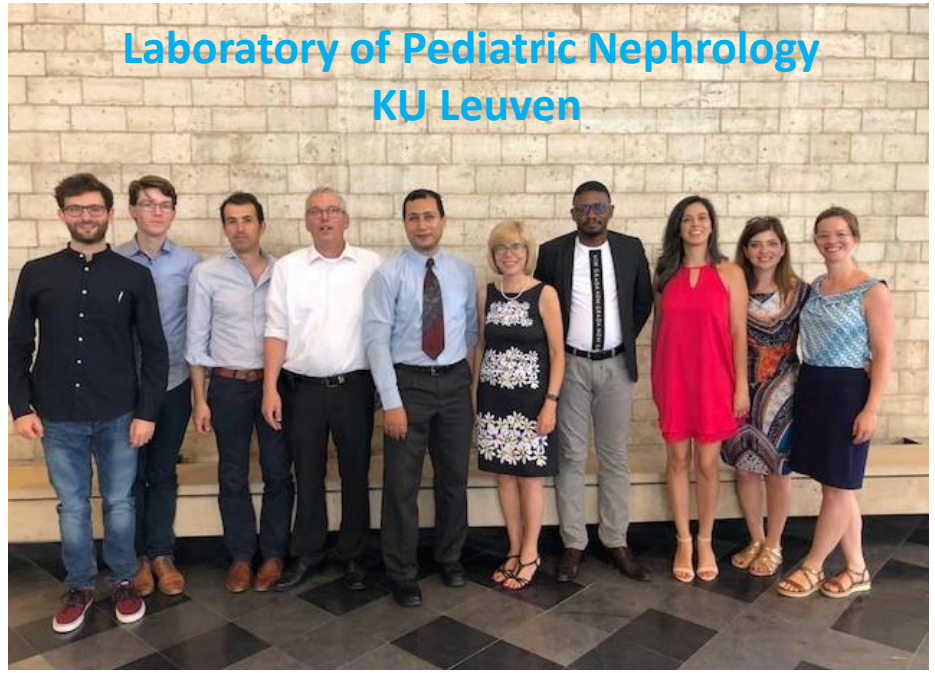

European Reference Networks
ERKNet
The European Rare Kidney Disease Reference Network

ERKNet

The European Rare Kidney Disease Reference Network

Coming soon…

Beata Lipska-Zietkiewicz

Schimke immune-osseous dysplasia

May 7, 2019, 4 PM CET

University Hospitals Leuven