3rd CNE International Cystinosis Conference

Leuven, Belgium

7-10 July 2022

Cystinosis Network Europe

Overview of cystinosis treatment in 2022

Elena Levtchenko

UZ LEUVEN

CYSTINOSE Groep

Nederland en Vlaanderen

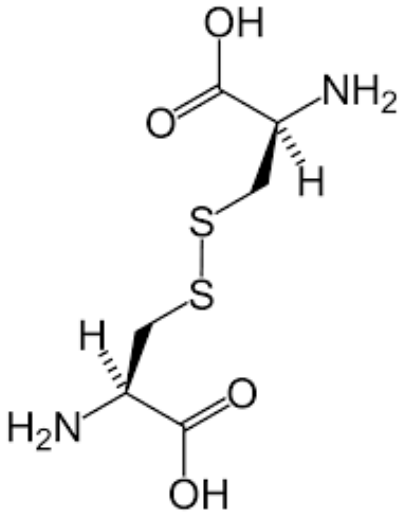
KU LEUVEN

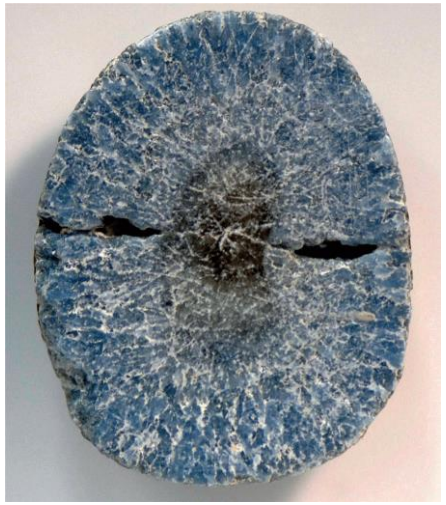
Overview of the lecture

- Cystinosis as a multi-system disorder
- Symptomatic treatment
- Renal replacement therapy
- Cysteamine treatment
- New therapies
- Take home notes

Cystine: first described amino acid

William Hyde Wollaston
(1766-1828)





Gordon Museum, King's College London

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

Thomas, K. *et al.* (2014)

nature REVIEWS UROLOGY

Wollaston W. On cystic oxide: a new species of urinary calculus. *Philos. Trans. R. Soc. Lond.* 100, 223–230 (1810).

First description of cystinosis

Emil Abderhalden
1877 - 1950

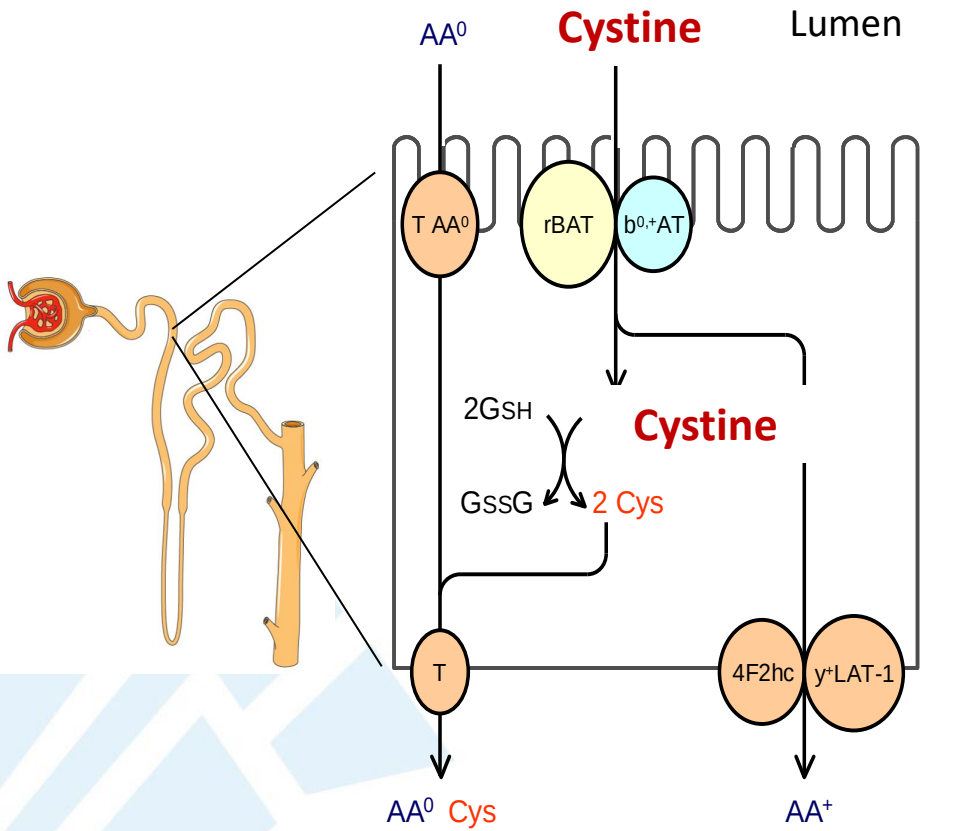
Abderhalden E.
Familiäre Cystindiathese.
Z. Physiol Chem 38: 557-561, **1903**

Autopsy of a 21-months-old child:

- Failure to thrive, poor growth
- Cystine crystals in the liver and spleen

Confusion between cystinosis and cystinuria

Cystinuria: kidney stone disease



Defect in cystine reabsoprtion

⇩

High cystine concentration in urine

⇩

Kidney stone formation

Courtesy F. Emma

Find a difference!

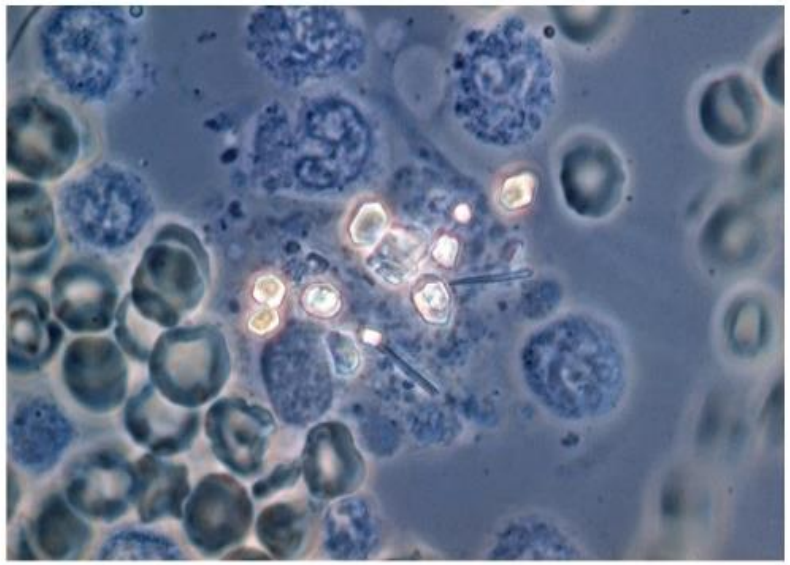
Cystinosis ≠ Cystinuria

Clinical symptoms	Cystinosis	Cystinuria
Growth retardation	**yes**	
Fanconi syndrome	**yes**	
Kidney stones	**no**	
Chronic kidney failure	**yes**	
Extra-renal symptoms	**yes**	

Biochemical basis of cystinosis

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

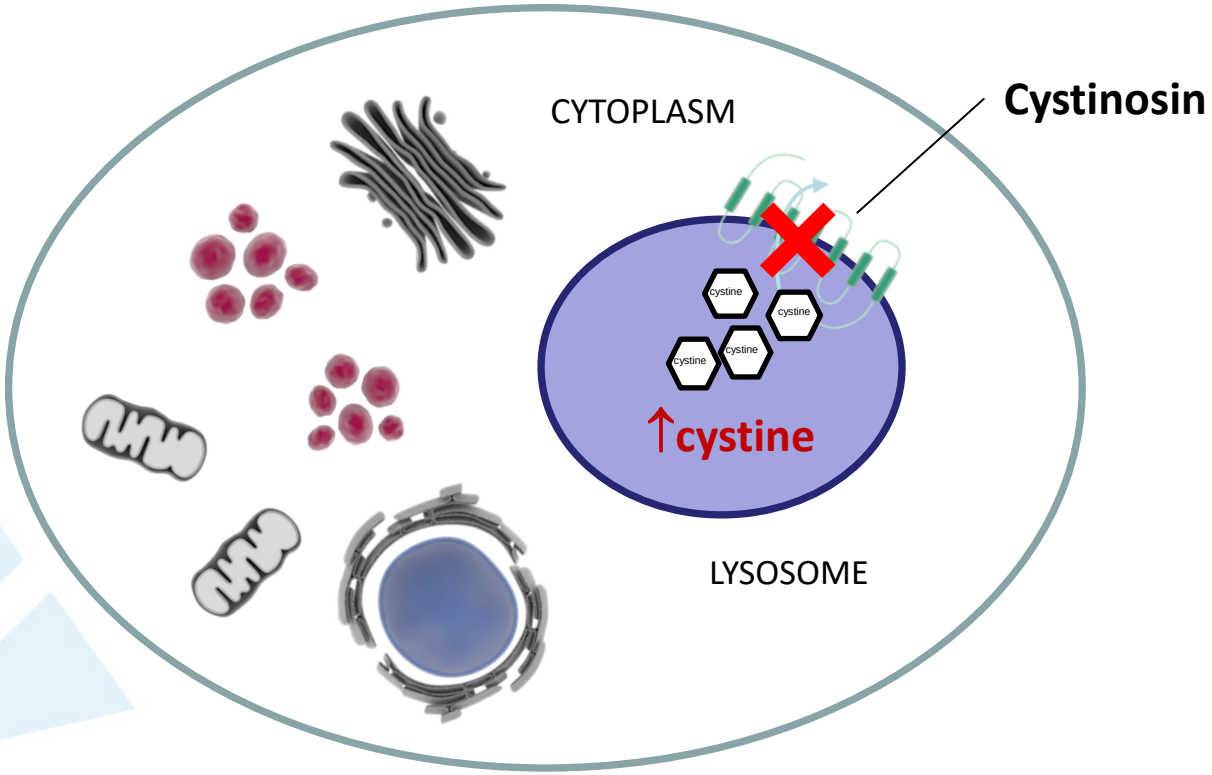
Science ***1967***



Bone marrow aspirate from 5 m old cystinosis patient. Seen unstained with phase microscopy.

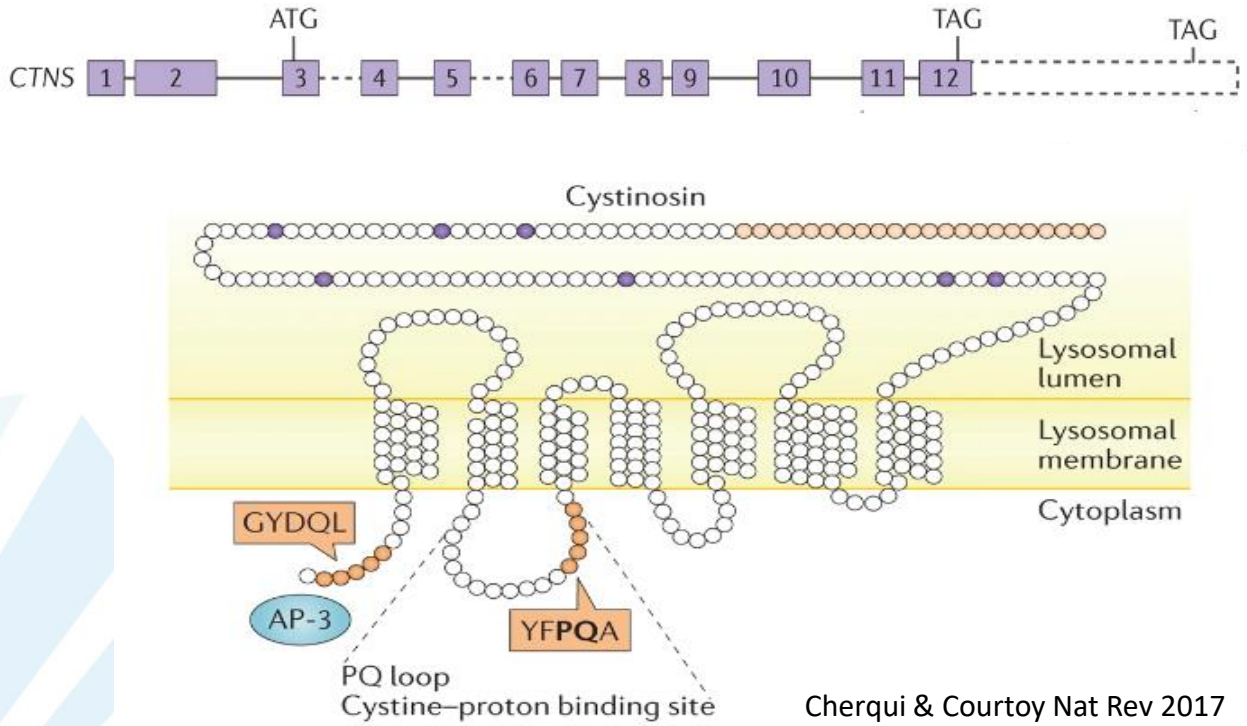
Cystine accumulation in cells

Cystinosis: lysosomal cystine storage disease



Courtesy K. Veys

Genetic basis of cystinosis: mutations in *CTNS* gene

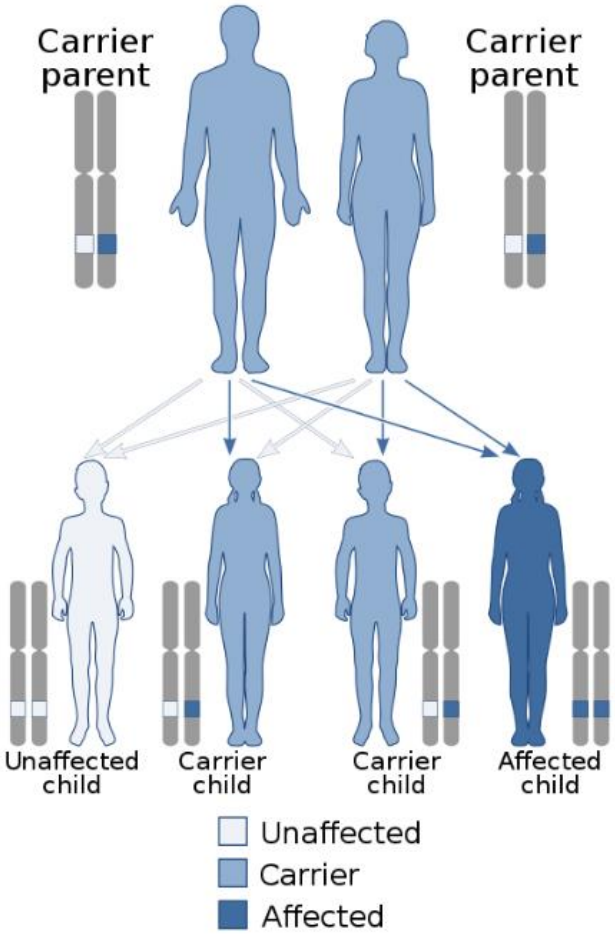


Cherqui & Courtoy Nat Rev 2017

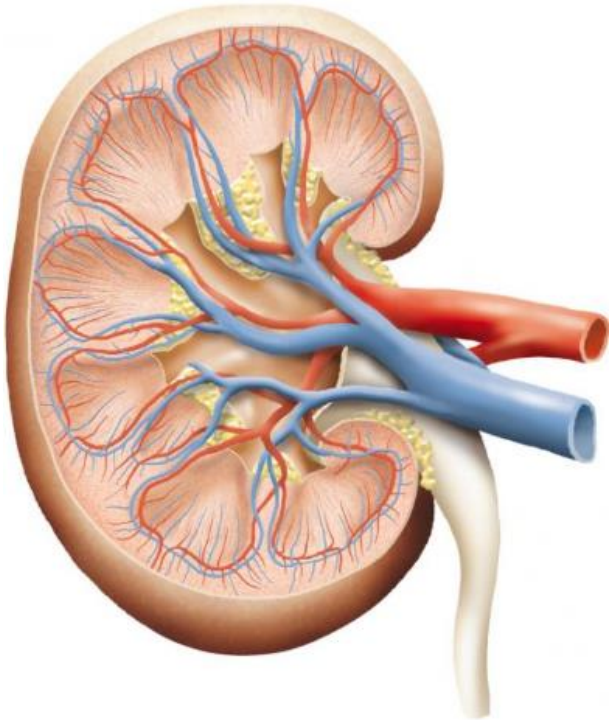
C. Antignac

Town et al.
A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis.
Nat Genet. 1998

Autosomal recessive inheritance in cystinosis



25% chance to have a child with cystinosis for each new pregnancy



Kidney is the first organ affected by cystinosis

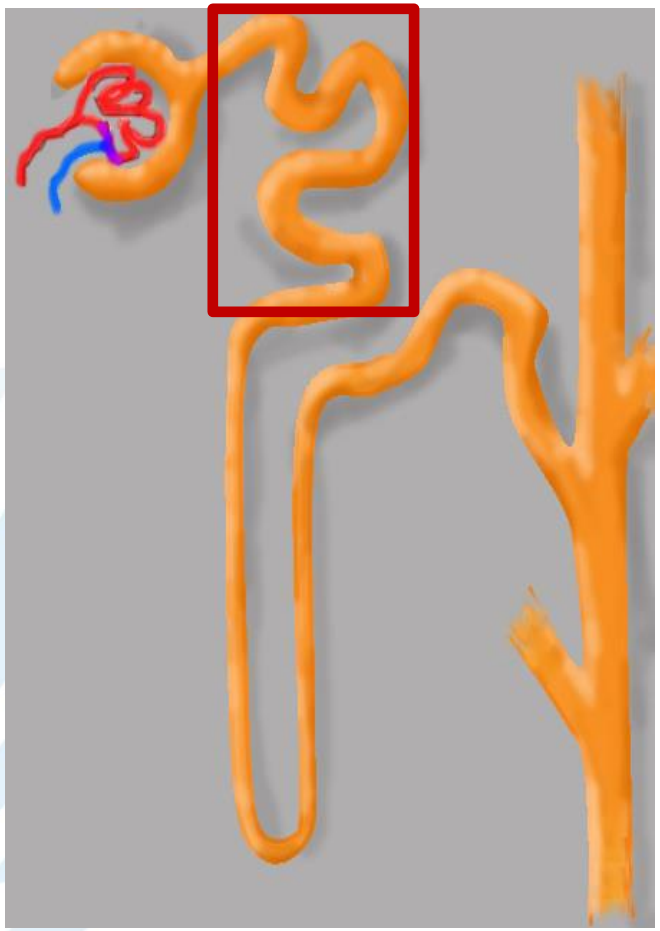
Mechanism of kidney disease in cystinosis

Kidney filter disease:
large proteins in urine

Proximal tubule (PT) disease:
renal Fanconi syndrome

Renal interstitial inflammation and scare formation:
progressive kidney function decline

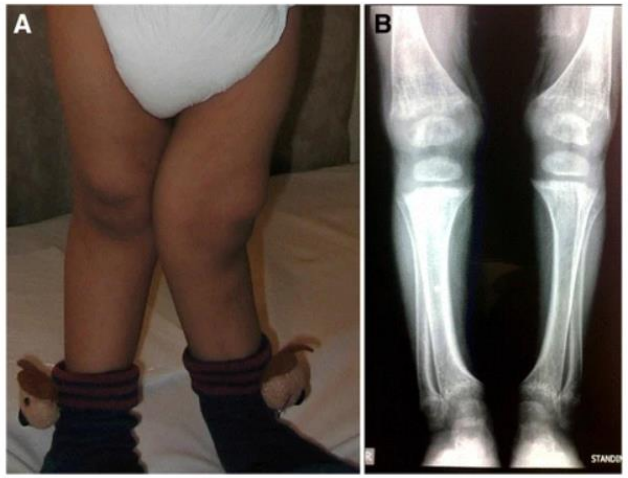
Renal Fanconi syndrome in cystinosis



- Dysfunction of renal proximal tubules:
  - High urine production
  - Urinary loss of amino acids, salts, small proteins, glucose, vitamins, hormones

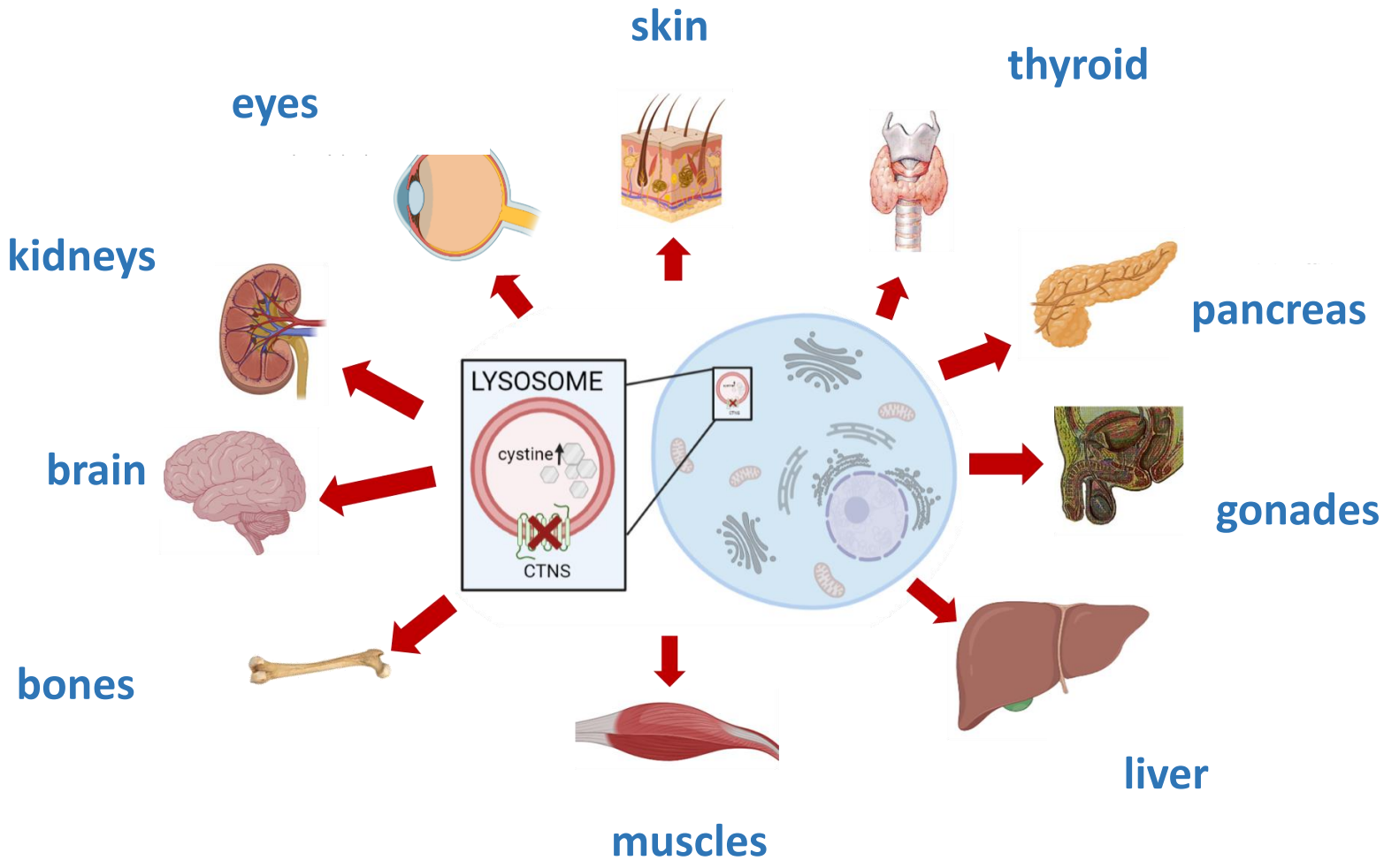
Clinical symptoms of renal Fanconi syndrome

- Excessive thirst
- Poor weight and height gain
- Vomiting
- Dehydration
- Constipation
- Rickets (bone disease)
- Low muscle tone
- Delayed motor development

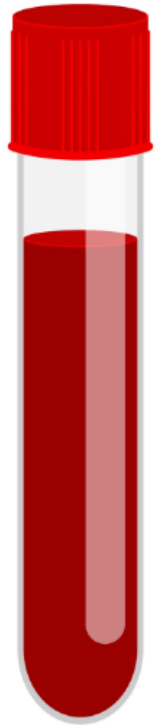


Elmonem *et al.* OJRD, 2016

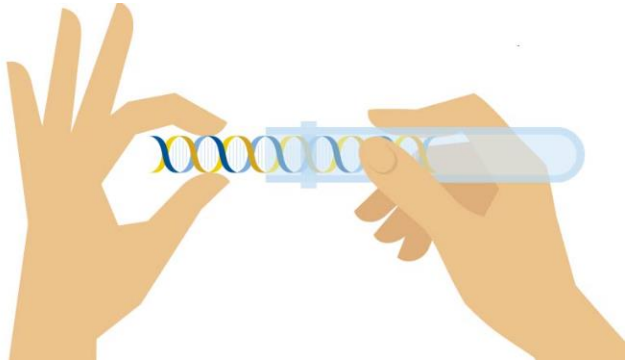
Cystinosis: a systemic disease



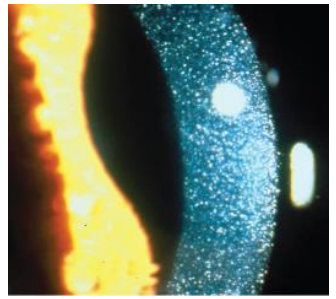
Diagnosis of cystinosis



Blood test
elevated WBC cystine



Genetic test
mutation(s) in *CTNS* gene



Eye test
corneal cystine crystals

Treatment of cystinosis

- **Symptomatic**
- **Renal replacement therapy**
- **Treatment with cysteamine**
- **Future therapies**

Symptomatic treatment

Access to water and toilet

Replacements of salts

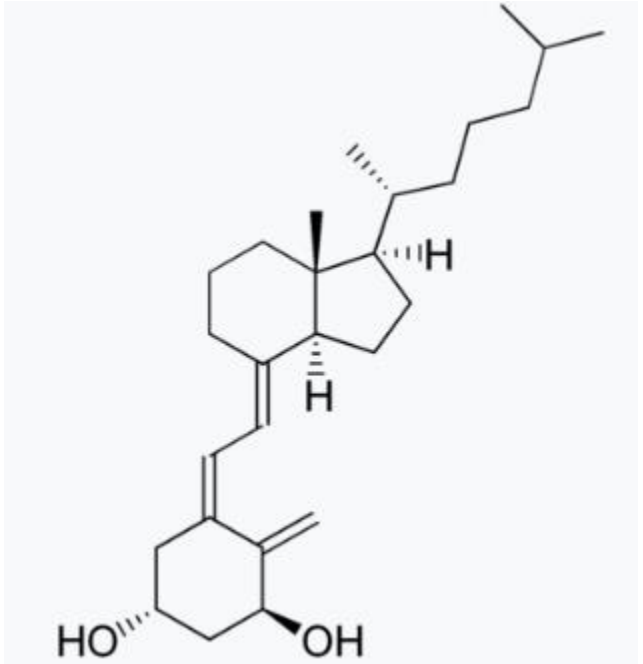
- Potassium
- Bicarbonate & citrate
- Phosphate
- (Sodium chloride)
- Calcium

Replacements of vitamins and hormones

- (Active) vitamine D

When required:

- Thyroid hormone
- Growth hormone
- Testosterone



alfacalcidol

Indomethacin

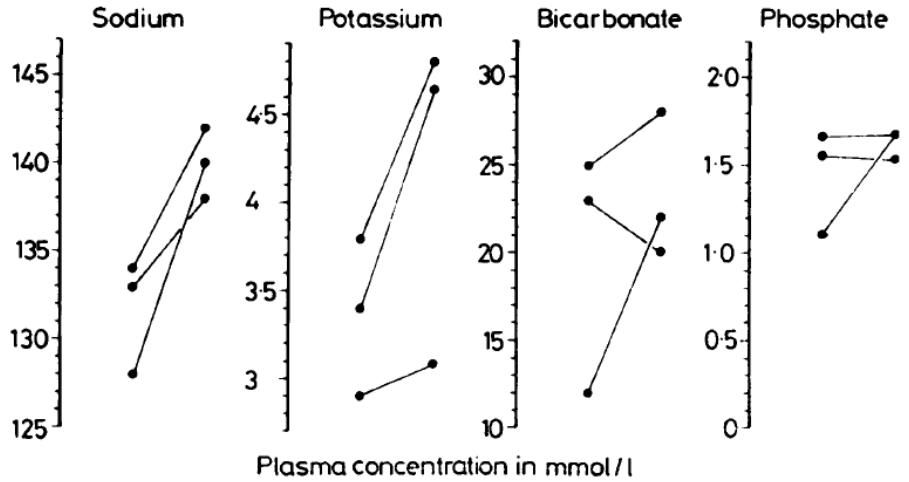
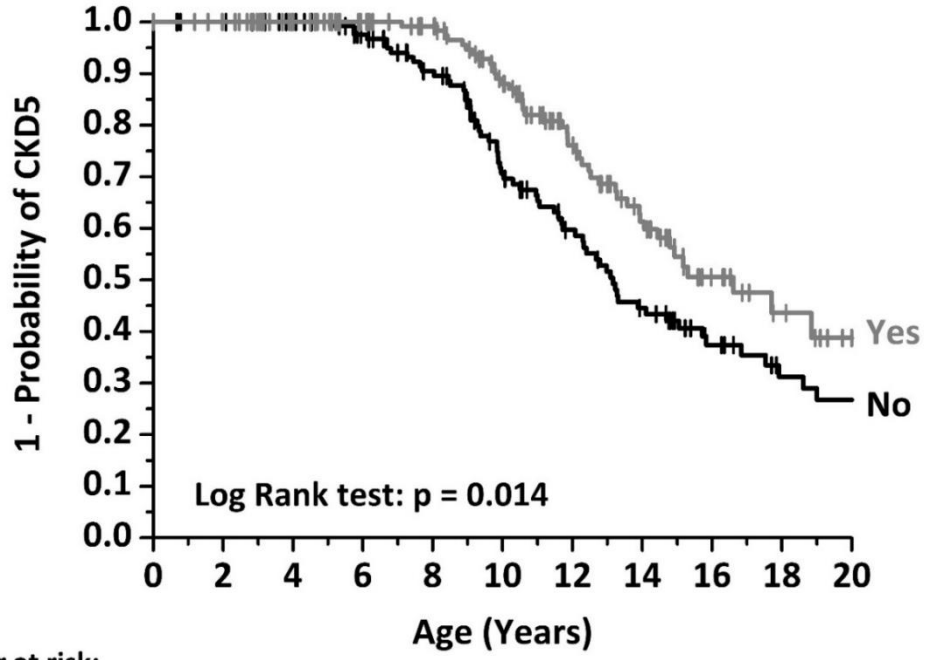


Fig. 3 ***Effects of 2 weeks' treatment with indomethacin on plasma electrolyte concentrations.***

- Reduces urinary losses due to renal Fanconi syndrome
- Dose: 1-2 mg/kg/day

Haycock et al. Arch Dis Child 1982

Indomethacin



Number at risk:

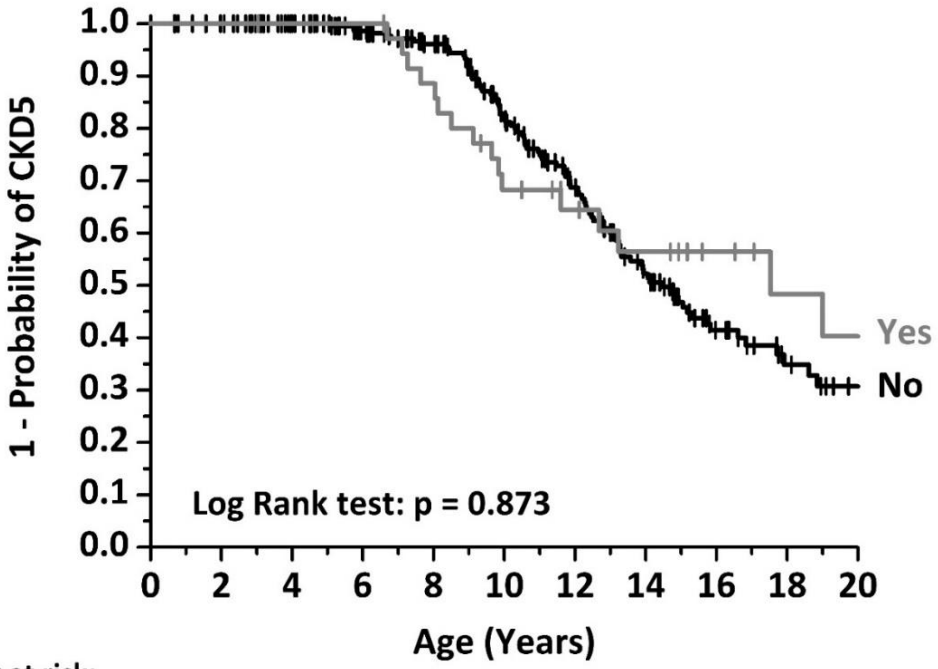
INDO: No	137	122	67	28	11
INDO: Yes	160	135	90	28	3

- Indomethacin has no impact on kidney function decline in cystinosis

Slide Courtesy F. Emma

data from EUNEFRON cohort

ACE inhibitors



Number at risk:

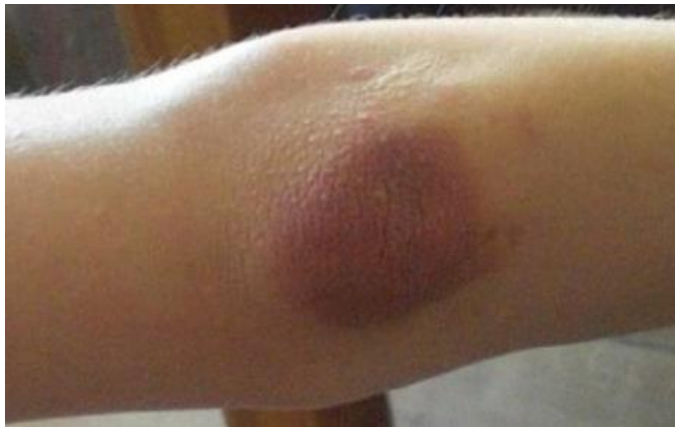
ACEi: No	261	222	135	45	10
ACEi: Yes	36	35	22	11	4

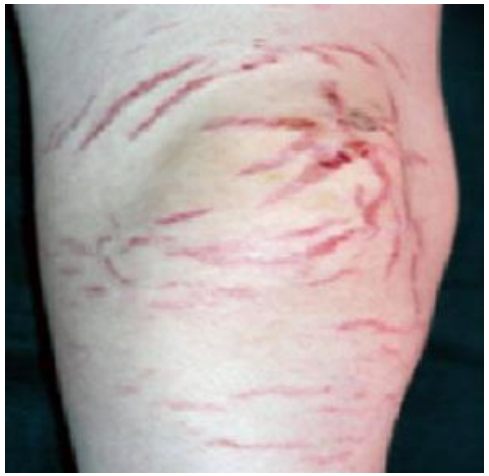
- Reduce proteinuria
- No proven evidence for positive effect on kidney function in cystinosis
- Should be stopped in case of gastroenteritis
- NOT in combination with indomethacin

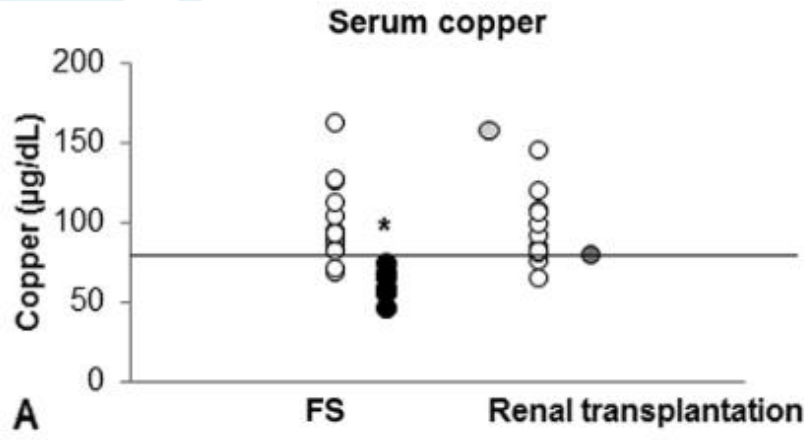
Slide Courtesy F. Emma

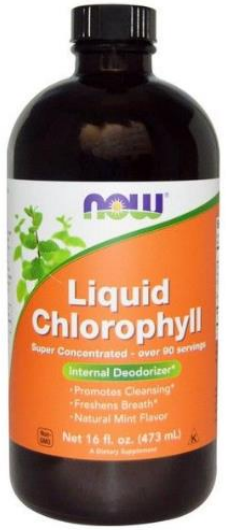
data from EUNEFRON cohort

Copper







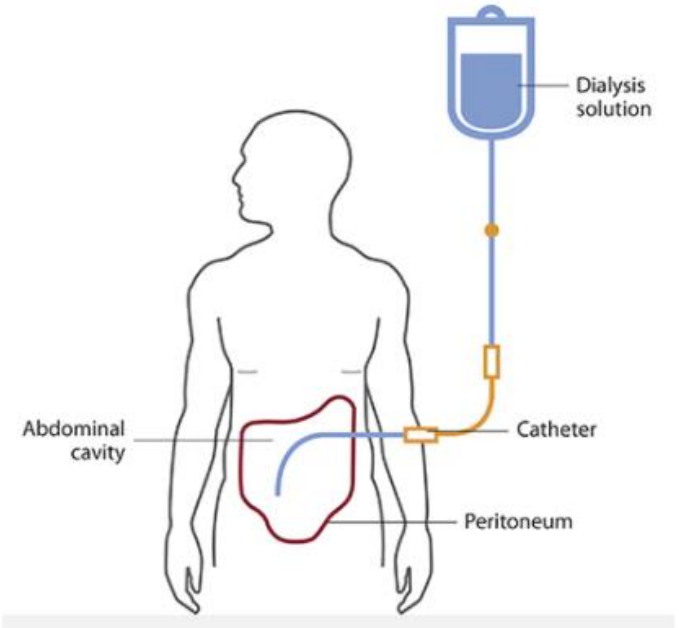


high copper content

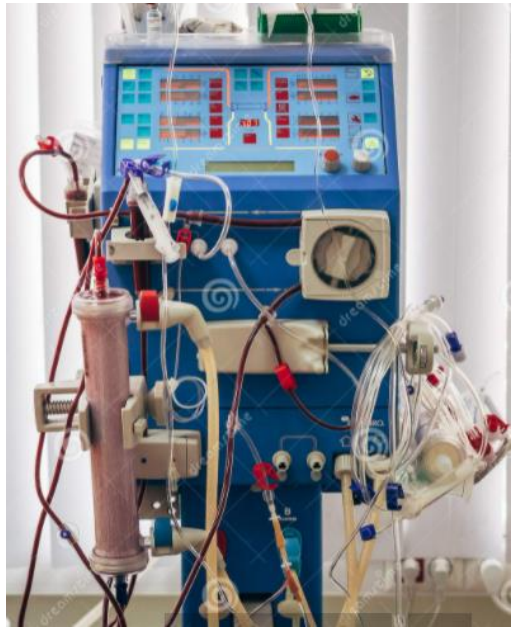
Besouw et al. 2011, 2013

Dialysis in cystinosis

Peritoneal dialysis (PD)



Hemodialysis (HD)

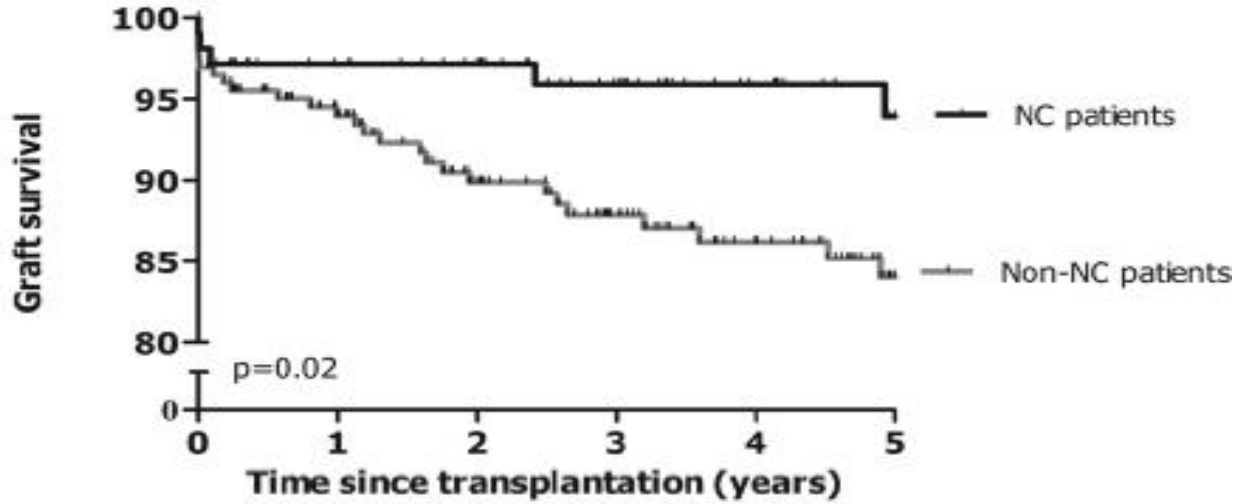


- Both PD and HD are possible
- No dose adjustment of cysteamine on dialysis is required

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
-
- 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

Kidney graft survival in cystinosis

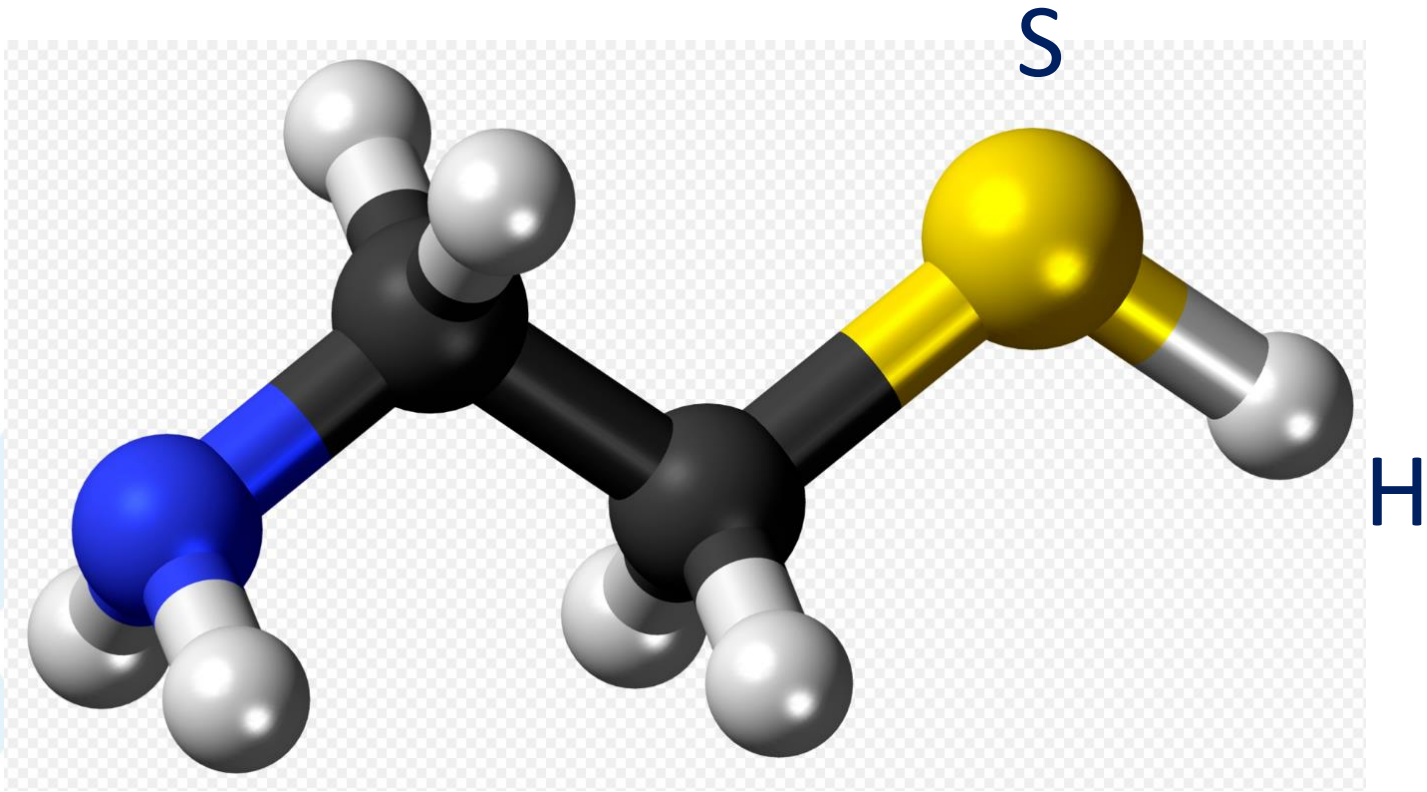


NC patients	122	92	85	71	56	47
Non-NC patients	235	175	144	117	94	67

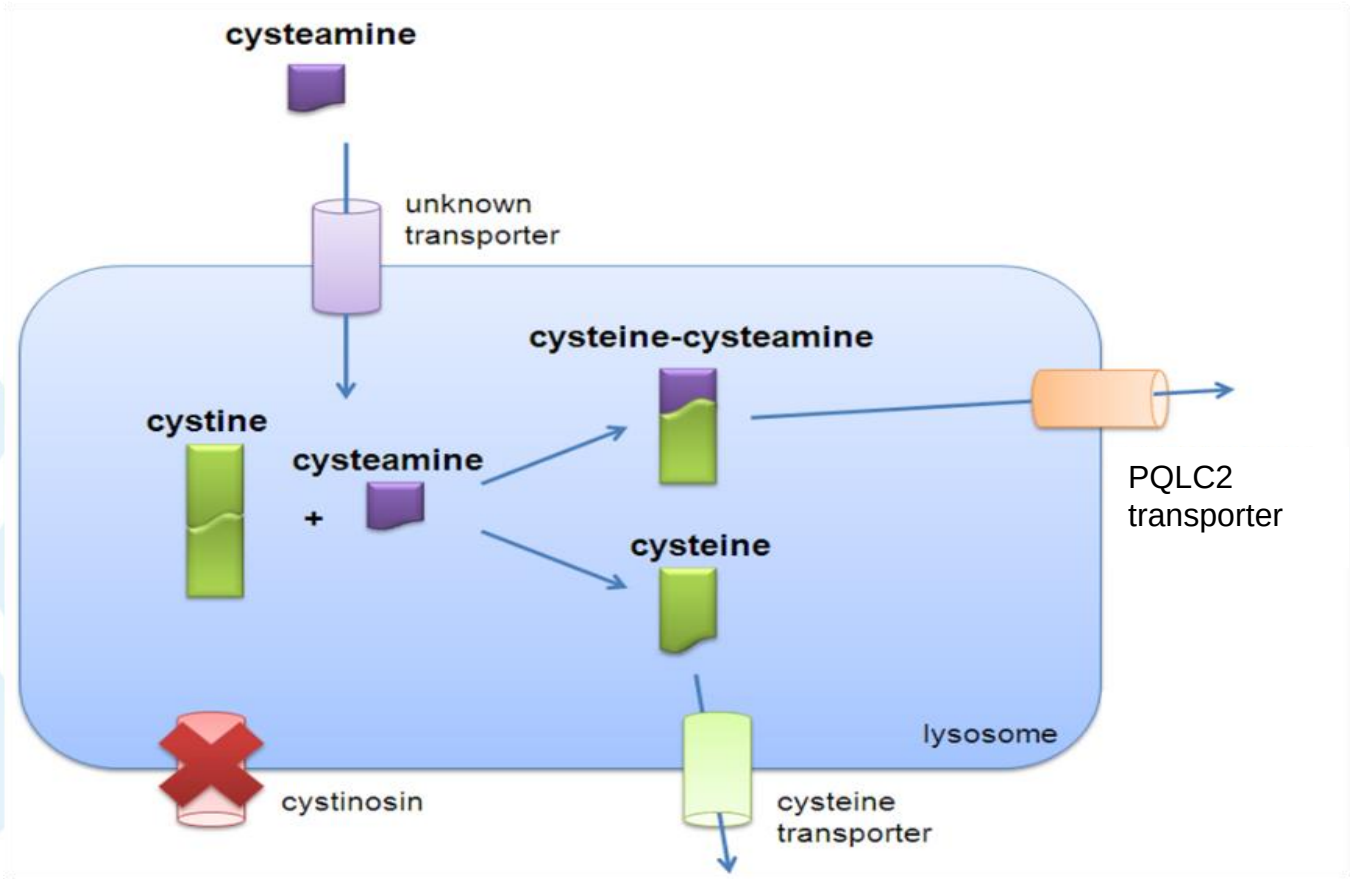
Figure 2. | Five-year graft survival of patients with nephropathic cystinosis (NC) and non-NC patients.

Van Stralen et al. CJASN 2011

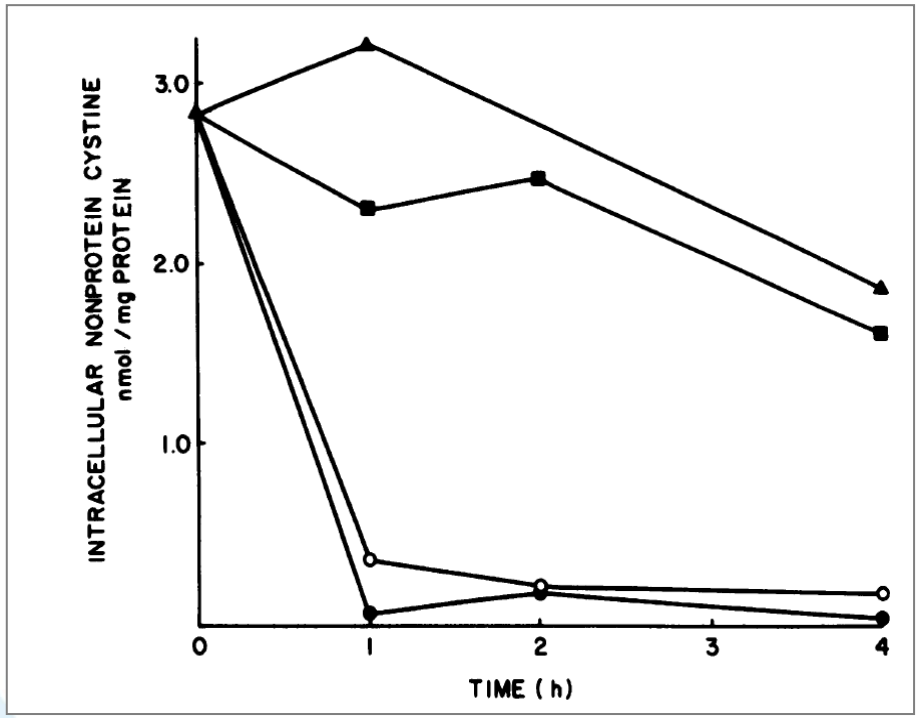
Cysteamine treatment



Cysteamine depletes intra-cellular cystine accumulation



Besouw et al. 2013

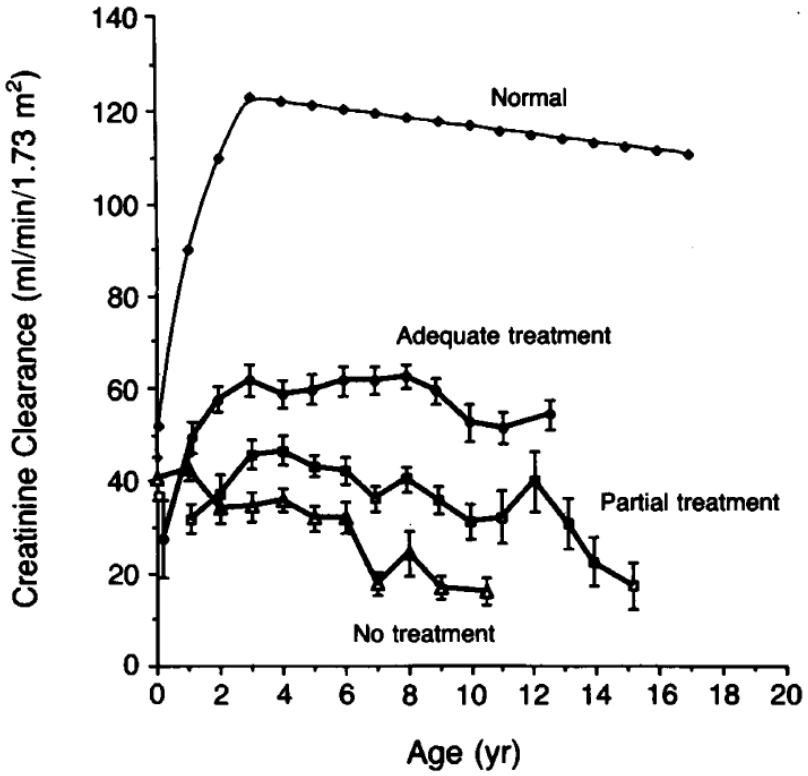


Cysteamine concentrations

- 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*

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

Cysteamine formulations

- Immediate release (IR) cysteamine bitartrate (Cystagon®) capsules 50 mg, 150 mg
  - < 12 yo: 1.3 g/m^2/day QID (every 6 hours, including the night)
  - > 12 yo and > 50 kg: 2 g/day QID
  - Maximum daily dose: 1.95 g/m^2
  - WBC cystine assay: 5-6 hours after last dose

- Extended release (ER) cysteamine bitartrate (Procysbi®): capsules 25 mg, 75 mg
  - 1.3 g/m^2/day BID (every 12 hours)
  - > 50 kg: 1g BID (every 12 hours)
  - Maximum daily dose: 1.95 g/m^2
  - WBC cystine assay: 12.5 hours after last dose

An international cohort study spanning five decades assessed outcomes of nephropathic cystinosis.

kidney INTERNATIONAL

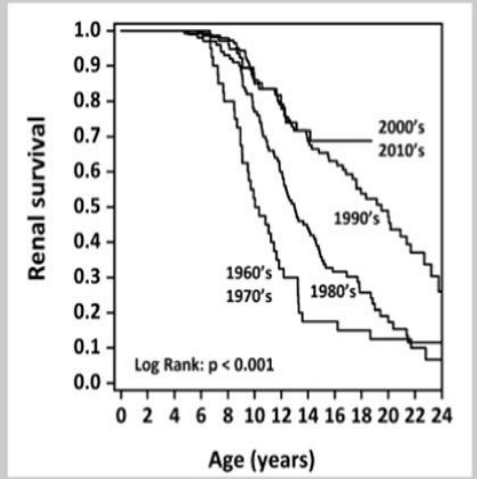
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

- Cystinosis is a rare disease secondary to mutations in the *CTNS* gene
- We collected data from a large cohort of 453 patients born between 1964 and 2016 and followed in:
  - Belgium
  - Germany
  - Austria
  - France
  - Italy
  - Spain
  - The Netherlands
  - Turkey
  - United Kingdom

- We investigated factors associated with kidney function and growth outcome

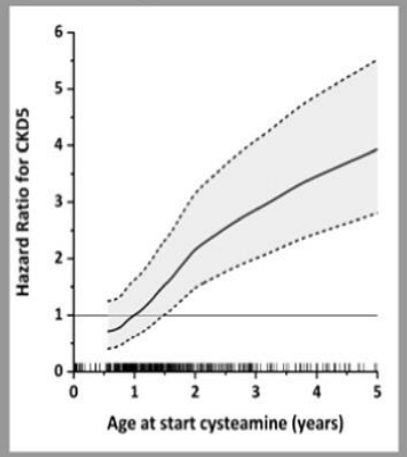
Results (1)

- Gain of 9.1 years in kidney survival from the 1970's to the 1990's
- No effect of the type of *CTNS* gene mutation



Results (2)

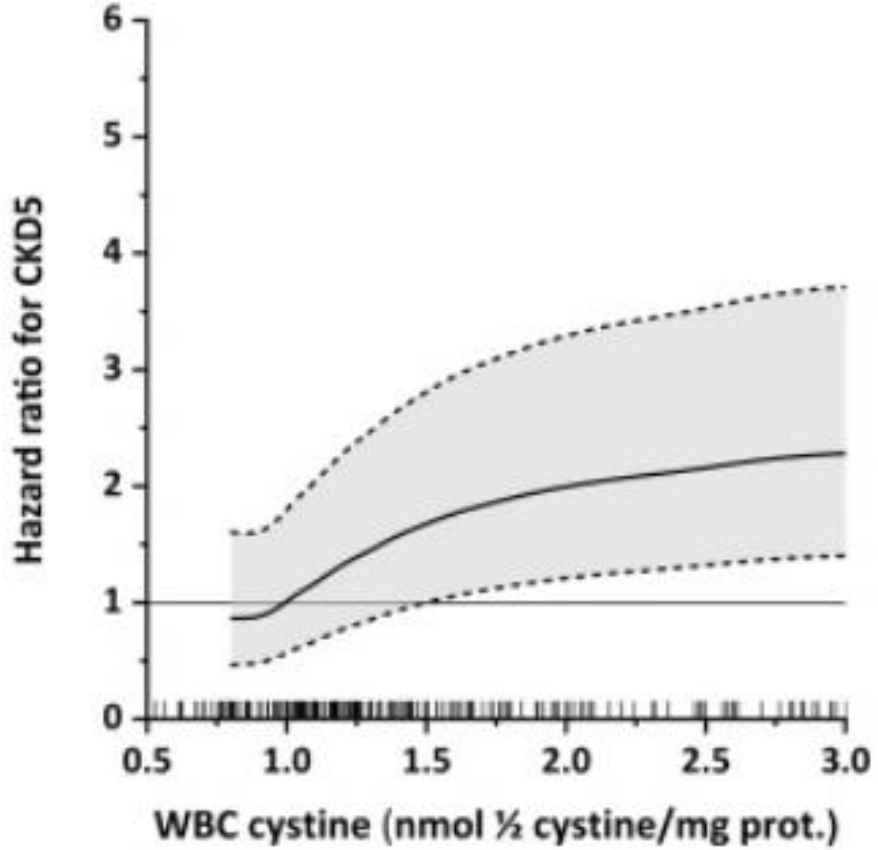
- Improved kidney survival was associated with the precocity of treatment with cysteamine and with average leukocyte cysteine levels
- Linear growth was equally improved in patients well treated with cysteamine



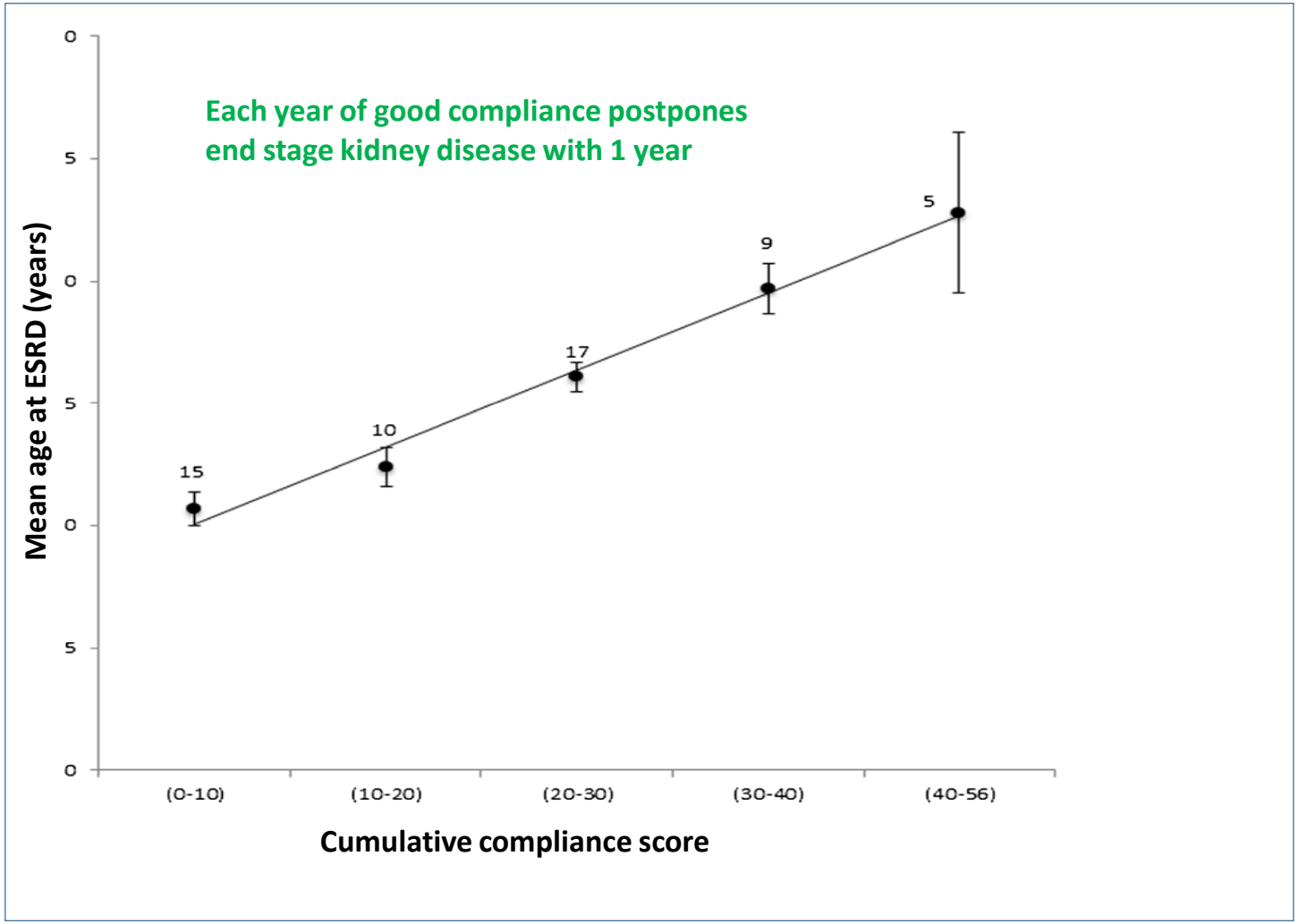
Emma Francesco et al, 2021

CONCLUSION: ***treatment with cysteamine has been the major factor responsible for improved kidney function survival in patients with nephropathic cystinosis over the past 50 years***

Start cysteamine immediately after birth might completely prevent kidney damage (Hohenfellner et al. 2022)



Emma et al. 2021



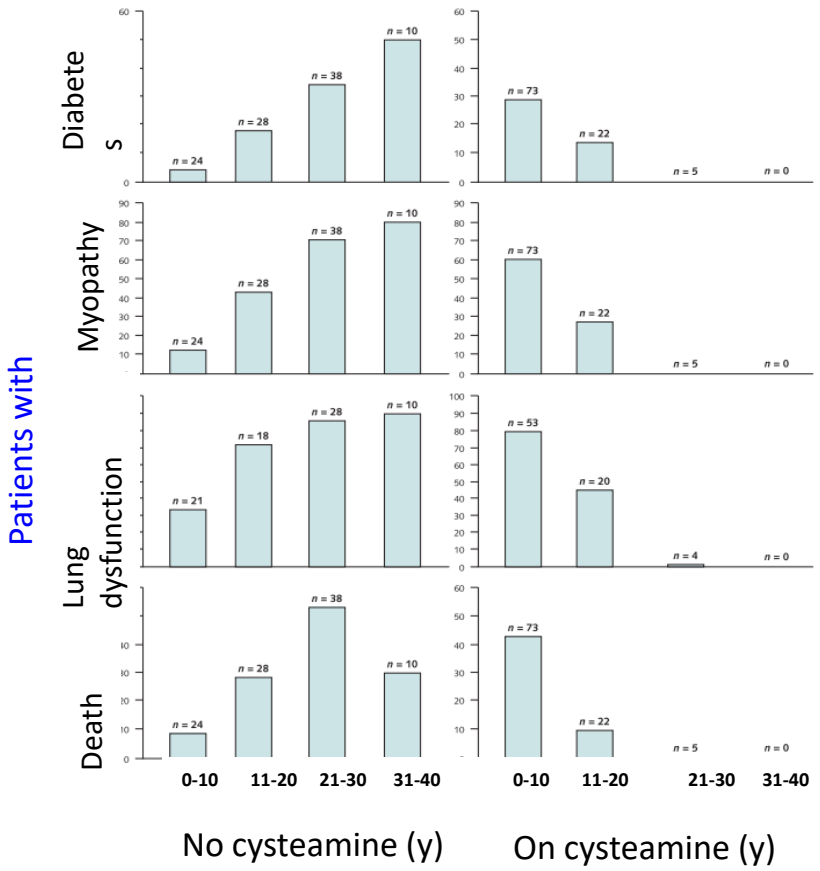
Nesterova et al. 2015

Cysteamine protects extra-renal organs

Gahl et al.
Nephropathic Cystinosis in Adults: Natural History and Effects of Oral Cysteamine Therapy
Ann Intern Med. 2007

N=100
Age: 26 ± 6.5 yo

Frequency of cystinosis complications

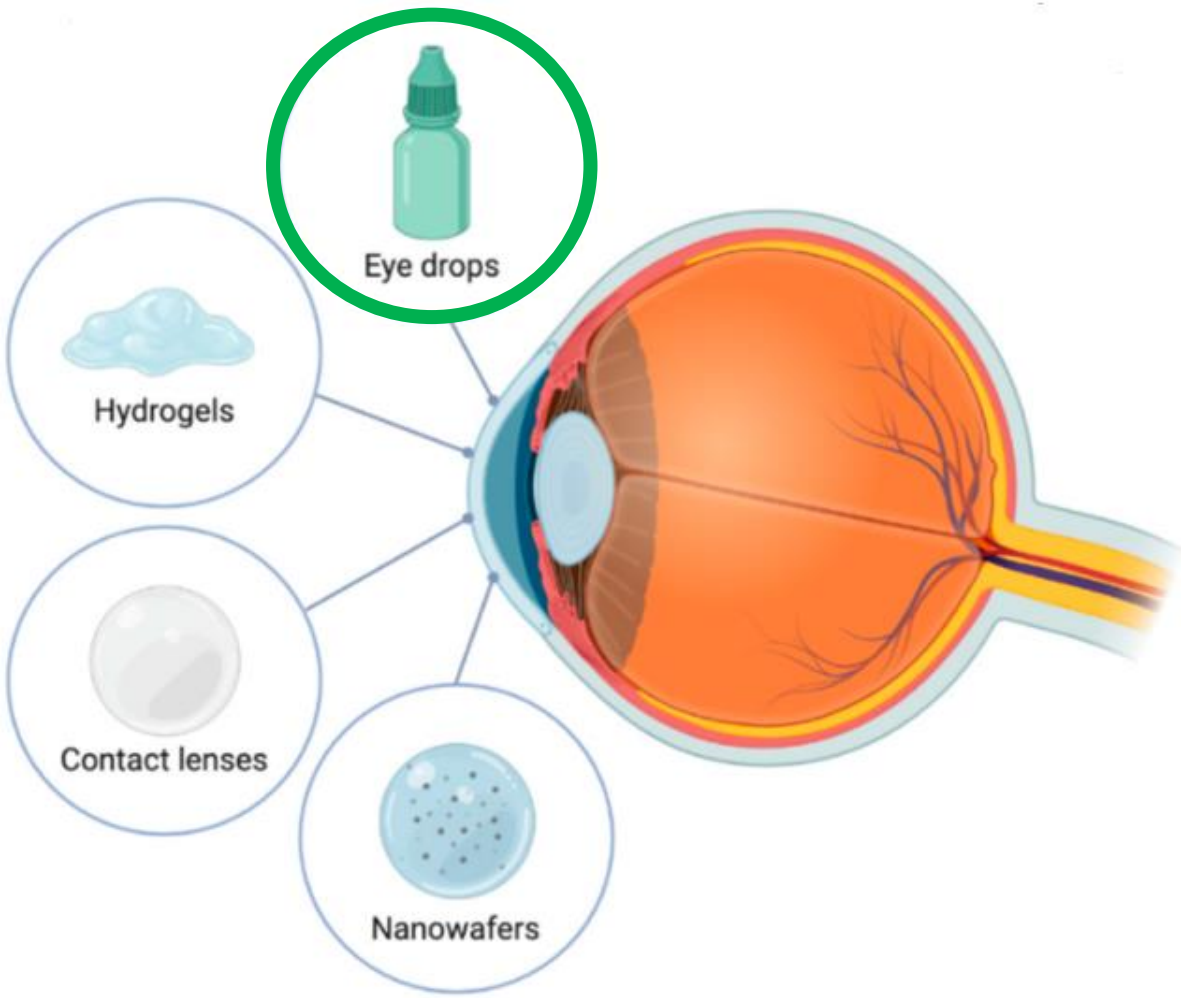


Cysteamine side effects

- Bad breath and sweat odor
- Abdominal complaints

- Neurological complaints
- Skin reactions

Topical cysteamine treatment



Castro-Balado et al. 2020

Future therapies

- Hematopoietic stem cell transplantation
- Protection of muscles and bones
- New cysteamine preparations
- Improving cellular functions in cystinosis beyond cystine accumulation
- Diet interventions
- Molecular therapies (gene repair, gene addition)

Take home messages

- Prognosis of cystinosis is substantially improved during last 30 years
- Early and consequent cysteamine treatment prevents or postpones most of complications
- Future therapies are under way

Achnoledgements

Leuven cystinosis clinical team

K. Veys
M. Van Dyck
D. Cassiman
A. Van Hulle
L. Willem
I. Casteels
K. Van Keer
L. De Waele

Leuven cystinosis research team

L. Van den Heuvel
K. Veys
F. Arcolino
S. Berlingerio
T. Bondue
I. Bongaers
S. Van Aarschot

International research partners

KU LEUVEN

R. Gijsbers
M. Sampaolesi
L. Medaer
P. De Witte